STUDY TO EVALUATE THE PREVALANCE OF HYPOMAGNESEMIA AMONG NEONATAL CONVULSIONS

Dissertation submitted to

THE TAMILNADU DR MGR MEDICAL UNIVERSITY

CHENNAI-600 032

in Partial Fulfillment of regulation for the award of

M.D. DEGREE IN PEDIATRIC MEDICINE

BRANCH - VII

DEPARTMENT OF PAEDIATRICS

COIMBATORE MEDICAL COLLEGE HOSPITAL

COIMBATORE

APRIL 2016

CERTIFICATE

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Page count:	94
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Submission date:	02-Oct-2015 06:33PM
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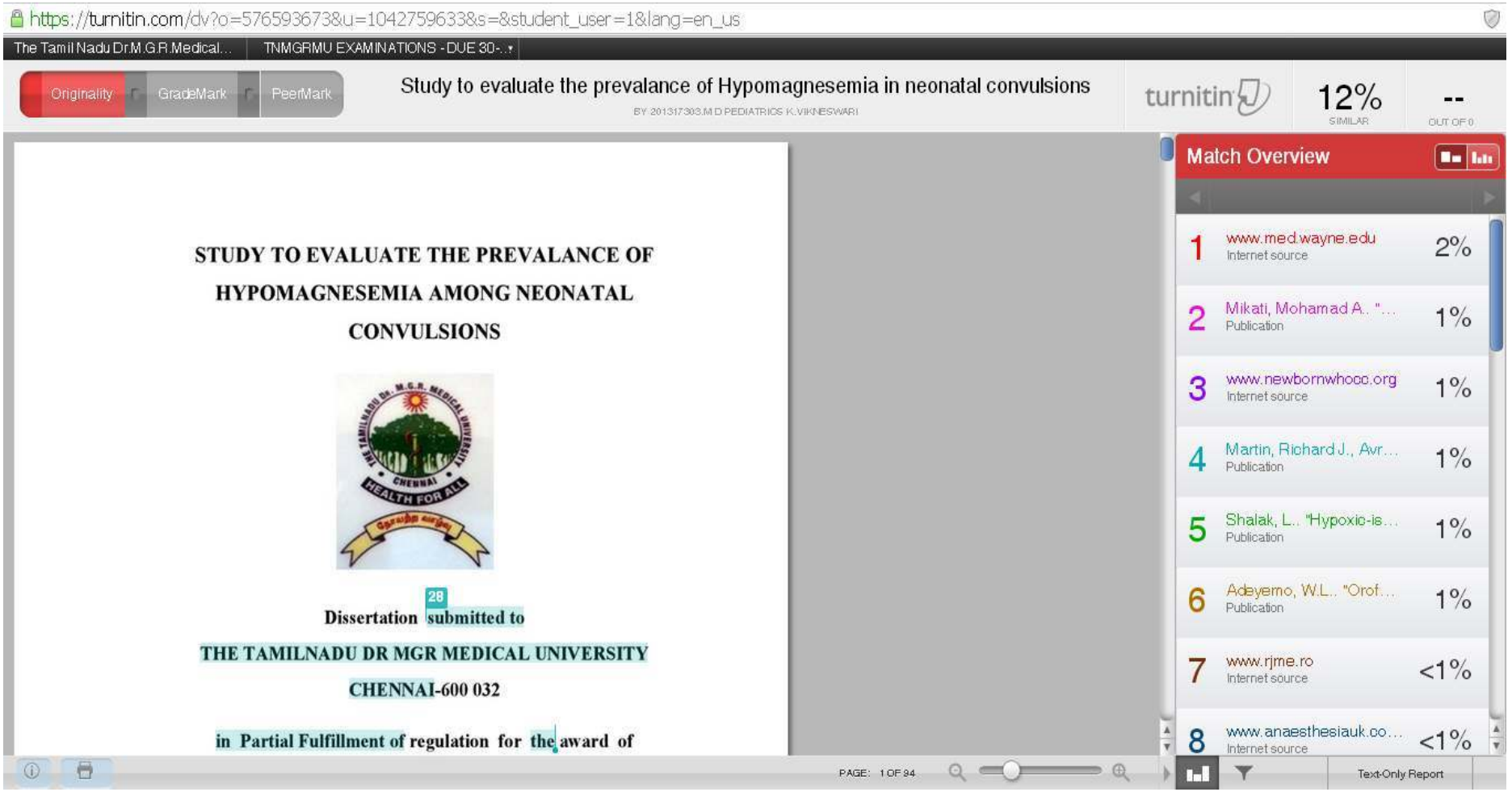
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DECLARATION

I Declare that this dissertation entitled " **STUDY TO EVALUATE THE PREVALENCE OF HYPOMAGNESEMIA AMONG NEONATAL CONVULSIONS "** has been conducted by me in NICU of , Coimbatore medical college hospital under the guidance and supervision of my guide Prof.Dr.V.Suganthi, M.D., DCH. It is submitted in part of fulfillment of the award of the degree of MD Pediatrics for the April 2016 examination to be held under The Tamilnadu Dr.M.G.R Medical University, Chennai. This has not been submitted previously by me for the award of any degree or diploma from any other university.

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ACKNOWLEDGEMENT

My sincere thanks to **Prof. Dr.Edwin Joe, M.D.,B.L.,** Dean, Coimbatore Medical College and Hospital for allowing me to do this dissertation and to utilize the institutional facilities.

I would like to express my sincere gratitude to **Prof. Dr.V.Suganthi ,** Professor of Pediatrics Coimbatore Medical College and Hospital for permitting me to undertake this study, and for guidance, invaluable helps, encouragement and support throughout the study.

I am extremely thankful to **Prof.Dr.Theenathayalan Kamalakkan M.D., DCH., Retd HOD., Prof. Dr.V.Booma MD., Prof.Dr.A.Lakshmanasamy.M.D.,DCH.,Prof.Dr.M.GeethanjaliMD., DCH.,** Associate Professors of Pediatrics for their guidance, encouragement and support throughout the study.

I would like to thank our registrar, **Dr.B.R.Sasikumar, M.D.,** for his valuable guidance and support for doing this study.

I extend my sincere thank to Asst. **Prof. Dr. N. Kumar M.D., Dr. S. Jayaprakash M.D., Dr. Uma shankar M.D., Dr. J. Ruckmani M.D., Dr.M. Senthil kumar M.D., Dr. V.K.Sathyan M.D., DM., and**

Dr.P.Senthilkumar M.D.,DM, Dr. P. Thiyagarajan M.D., DCH., for their invaluable suggestion, help and support throughout the study.

I sincerely thank **Mr.JOSHUA ALLEN SHEPHERD**, Statistician for his valuable help.

I sincerely thank all the parents who consented to participate in the study and also thank Staff nurses of NICU Coimbatore medical college Hospital without their support sampling could have been difficult.

I would also like to thank my parents and friends for their support throughout the study period without which this project would have been impossible.

Finally , I thank THE ALMIGHTY for all he has done to me and I pray for HIS continued blessings.

DR. VIKNESWARI K

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ABBREVIATION

Mg	Magnesium
Ca	Calcium
iCa	Ionised calcium
iMg	Ionised magnesium
NMDA	N-methyl D Aspartate
CNS	Central nervous system
NICU	Neonatal intensive care unit
K	Potassium
Na	Sodium
P	Phosphorus
EEG	Electroencephalogram
GTS	Generalized tonic seizures
HIE	Hypoxic ischemic emcepalopathy
ATP	Adenosine tri phosphate
GABA	Gamma amino butyric acid
SGA	Small for gestation
PTH	Parathormone
CT	Calcitonin
IL/TNF	Interleukin/ tumor necrosis factor

ABSTRACT

BACKGROUND AND OBJECTIVES:

Neonatal seizures are clinically significant because very few are idiopathic. Further investigation leading to prompt diagnosis of the underlying condition as well as associated biochemical abnormality is important for specific treatment. Recognition of hypomagnesemia and hypocalcaemia is important for therapeutic implications.

Objectives: To evaluate the prevalence of hypomagnesemia in neonatal seizures, To evaluate the prevalence of hypocalcaemia and rate of association of hypomagnesemia with hypocalcemia.

METHODOLOGY:

Our study is an observational study included 150 neonates based on inclusion and exclusion criteria defined , presenting during the period of one year from July 2014 to July 2015.Then relevant investigations including biochemical parameters were done and etiology of neonatal seizures and their associated biochemical abnormalities were diagnosed.

RESULTS:

The prevalence of hypomagnesemia among 150 selected neonates with seizures is 4.6% and prevalence of hypocalcemia is 31.3%. Prevalence of Combined hypocalcemia with hypomagnesemia 4% and isolated hypomagnesemia is 0.6%. Association of hypomagnesemia with hypocalcemia is 83% which is statistically significant.

CONCLUSION:

Hypomagnesemia as isolated abnormality for cause of seizure, or as associated abnormality in underlying etiology is rare. But 83% of hypomagnesemia is associated with hypocalcemia implying the interrelation in pathophysiology. So in documented hypocalcemia there is a need to estimate the levels of magnesium to find the associated hypomagnesemia because treatment of hypomagnesemia is definitive with magnesium salts.

KEY WORDS:

Hypomagnesemia, Hypocalcemia, Neonatal seizures, Hypomagnesemia with Hypocalcemia, Metabolic abnormalities.

INTRODUCTION

Neonatal seizures are sometimes the only clinical[1] sign of the presence of CNS disorders in the neonate. Thus it may indicate the presence of a potentially treatable cause and should promote an immediate search for the cause and for starting appropriate therapy.

It is essential to determine the etiology of seizure at the earliest because it gives an opportunity to treat the seizure actively and promptly and avoid preventable morbidity, mortality and sequelae associated with it.

In our modern sophisticated medicine era, though the mortality due to seizures has decreased over years, the prevalence of long-term neurodevelopment adverse outcome[2] has largely remained unchanged. Inadequate and improper management of seizures `could be the reason for this.

Even with established etiology for neonatal seizures there is significant contribution to the seizure activity by the underlying biochemical abnormalities. So early recognition of associated biochemical abnormalities and appropriate treatment is essential for better outcome.

Among the metabolic causes of seizures good prognosis[3] are with hypoglycaemia, hypocalcemia and hypomagnesemia. But most of hypocalcemic seizures are accompanied by hypomagnesemia, but Magnesium levels are rarely investigated in resource restricted hospitals and Magnesium has neuroprotective role.

Interest in the physiology and chemistry[4] of the mineral magnesium has gradually increased over a period of time. Mg is involved in the activation of Na/K ATPase pump of cell membranes hence it maintains the electrical potential across the membrane, and Mg is also needed for enzymes that play a role in cell membrane stability and nerve conduction, and hypomagnesaemia leads to nerve and muscle excitability.

It has been suggested that low serum Mg has occasionally been associated with significant effects on the central nervous system especially in epilepsy. A positive correlation of the hypomagnesemia with the severity of epilepsy was also found and more severe the epilepsy, the lower was the plasma Mg.

Magnesium acts on the nervous system by reducing the release of acetylcholine at the level of neuromuscular junction[5] by antagonising calcium ions it reduces the excitability of nerves. Thus it acts as an anticonvulsant, and also reverses the cerebral vasospasm.

In our NICU, seizures are the most common cause for admission and it occupies a significant proportion of adverse neurological outcome in babies discharged. So in order to know the prevalence of hypomagnesemia in neonatal seizures in our setup I have taken this study.

Hypocalcemia in a significant proportion of seizures is associated with hypomagnesemia and treatment with only calcium will worsen the seizure activity. But when magnesium is administered the minimum mineral requirement are met and this itself results in increased calcium retention. So on administering magnesium both hypocalcemia and hypomagnesemia is corrected. Thus how often hypomagnesemia associated with hypocalcaemia has to be studied.

In this study I have concentrated on the associated metabolic abnormality in an established cause of neonatal seizures particularly on hypomagnesemia and hypocalcemic-hypomagnesemia

AIMS AND OBJECTIVES

PRIMARY OBJECTIVE:

1. To evaluate the prevalence of hypomagnesemia in all neonates admitted with seizures by analyzing the serum magnesium levels

SECONDARY OBJECTIVE:

1. To evaluate the prevalence of hypocalcaemia and rate of association of hypomagnesemia with hypocalcemia within the study group

REVIEW OF LITERATURE

Magnesium (Mg) is third common intracellular cation[5] and fourth common cation in the body. It is mainly found in muscles, other soft tissues, bones and erythrocytes.

As early as 1944, a correlation between magnesium, tetany, and petitmal seizures was reported[6]. Since then numerous studies have been made in the deficiency of magnesium by many investigators. Beck observed in 1952 that a deficiency of magnesium might well produce effects similar to hypophysectomy. Martin, Meke and Wertman[7] did a very comprehensive study on the clinical influence of magnesium metabolism, and again noted that in the state of epilepsy, there was a deficiency of serum magnesium. Numerous investigators have noted a form of tetany and occasional petit mal in this syndrome where a low magnesium intake was noted. Clinical observations in man[8-10]and experimental investigations in animals[17] have shown that magnesium (Mg) depletion causes a marked irritability of the nervous system, eventually resulting in epileptic seizures.

The possibility of seizures due to hypomagnesemia provoked the interest to study the metabolism of Mg in the seizures , and a trend of low magnesium was found.[11-15] In successive studies, Hirschfelder and Haury[16-19] found a lowering of Mg and a rise of potassium in the blood of epileptic patients, leading to a definite increase in the K/Mg ratio, proportional to the severity of the disease. Concerning the metabolism of magnesium in the cerebrospinal fluid, Cohen,[20] McCance and Watchorn[21], and Greenberg andAird[22] found in epilepsy the same range of magnesium levels as in other nervous diseases. Hirschfelder and Haury[23] found low concentrations of Mg in the cerebrospinal fluid of epileptic patients, though the levels were higher than in the blood

Epidemiology

The National Neonatal Perinatal Database, which collected data from 18 tertiary care units across the country, has reported an incidence of 10.3 per 1000 live-births. The incidence was found to increase with decreasing gestation and birth weight - for example, preterm infants had almost twice the incidence when compared to term neonates[24] (20.8 vs. 8.4 per 1000 live-births) while very low birth weight infants had more than 4-fold higher incidence (36.1 per 1000 live-births).

DEFINITION OF SEIZURES

A seizure is defined clinically as a paroxysmal alteration in neurologic function, i.e. motor, behaviour and/or autonomic function. This definition includes[25]:

1. Epileptic seizures: phenomena associated with corresponding EEG seizure activity e.g. clonic seizures

2. Non-epileptic seizures: clinical seizures without corresponding EEG correlate e.g. subtle and generalized tonic seizures

3. EEG seizures: abnormal EEG activity with no clinical correlation.

CHARACTERISTICS IN NEWBORN SEIZURES

A seizure is the most frequent sign of neurologic dysfunction in the neonate. Since seizures may be the only sign of a central nervous system disorder, their recognition is important[26].

The neonatal period, unquestionably is the most hazardous period of life, never again in life an individual is confronted with more dramatic changes than in transition from dependent intrauterine existence to independent post natal life. The new born brain responds in the form of

convulsion even for a minor insult, because of the immaturity of the nervous system.

The pattern of newborn seizures varies from the of seizure in adults due to the immaturity in anticonvulsant network in the developing brain.

The precise reason must relate to developmental state of nervous system in the prenatal period. The most common neuroanatomical processes occurring in that period are organizational events. This process must be highly significant in providing cortical organization to propagate and sustain a generalized seizure. Such a degree of cortical organization is apparently not present in human neonates[27].

The presentation of a newborn with seizure represents a true emergency[28] and frequently indicates significant neurological dysfunction or damage to the immature nervous system[29]. The neonate is at particular risk for development of seizures because of metabolic, anoxic, structural and infectious causes, although no cause can be identified in one fourth of cases. Clinical presentation of seizure, etiology, management and diagnosis of seizure differ markedly to convulsions occurring in older children[30.]

CLASSIFICATION OF NEONATAL SEIZURES

The international classification of epileptic seizures does not apply to newborn seizures[31] because neonates are unstable to sustain organized discharges and do not manifest generalized tonic clonic seizures.

Any abnormal, repetitive and stereotypic behaviour in neonates should be evaluated as possible seizure[32].

Volpe in 1989 gave [8-10] very simple and effective classification i.e., he sub classified seizures into four types: subtle, clonic, tonic and myoclonic[33].

This classification is in use recently.

Hill and Volpe in year 1994 classified neonatal seizures into following types:

1) Subtle

2) Tonic

   a. Generalized

   b. Focal

3) Clonic

a. Multifocal

b. Focal

4) Myoclonic

a. Focal

b. Multifocal

c. Generalized.

SUBTLE SEIZURES:

The most common form of neonatal seizures is subtle seizures. Available information from studies using EEG simultaneously with slow recording or direct observation suggests that:

1. It is more common in premature infants.

2. Many clinical phenomenon's which are subtle in full term infants are not always associated with abnormal EEG discharge. Eye opening, ocular movements, peculiar extremity movements (e.g., resembling boxing or hooking movement), mouth movements and apnea have been documented in association with EEG seizure activity, usually in temporal leads.

In study of Mizrahi and Kellaway[34], 22 infants of which 19 (85%) were more than 36 weeks of gestation exhibited paroxysm of ocular movements such as eye blinking, oral buccal lingual movements, pedalling or stepping movements or rotator arm movements with an inconsistent association with EEG seizure activity.

The data appear to indicate that much caution should be used in attributing an epileptic origin to many subtle clinical phenomenon, particularly in full-term infant and particularly if these phenomenon are the only manifestation of seizure in the infant. Although apnea has been demonstrated as a seizure manifestation in the premature newborn [35], vast majority are non-epileptic in origin. In 14 of the 21 infants studied by Watanabe et al[36] the infants exhibited other subtle phenomenon during the apneic seizure e.g., staring, mouth movements. Apnea as a seizure with EEG activity is less likely to be associated with bradycardia than in non-convulsive apnea.

CLONIC SEIZURES:

Clonic seizures (Fig 1) which involves clonic movements in the newborn are characterized by rhythmic and usually slow activity. It can be focal or multifocal.

Infants commonly are not clearly conscious during or after the focal seizures and the neuropathology is often focal in nature e.g., cerebral infarction. However, it is important to recognize that focal clonic seizures may occur with metabolic encephalopathies in the newborn.

Fig 1: Tonic and Clonic phase of neonatal seizure

TONIC SEIZURES:

Tonic seizures are clinical episodes most common of which are unassociated with time-synchronized EEG discharges. Two types of tonic seizures must be differentiated - focal and generalized. Generalised tonic seizures are more common in newborn than focal one.

Focal tonic (Fig 2) seizures are characterised by sustained / asymmetric posturing of the limb, neck or trunk. In contrast to generalized tonic seizures, focal are consistently associated with EEG activity.

GTS is characterized mostly by tonic extension of upper and lower limbs. Approximately 85% of such clinical seizures are not accompanied by electrical seizure activity.

Fig 2: Tonic seizures in new born

MYOCLONIC SEIZURES:

Myoclonic seizures are clinical episodes that as a group are most commonly unassociated with time synchronized EEG discharges. Myoclonic movements are distinguished from clonic by its characteristic more rapid speed of the myoclonic jerks, and it has predilection for flexor group of muscles .

Three categories should be distinguished

(1) Focal

(2) Multifocal

(3) Generalized.

SEIZURES VERSUS JITTERINESS / NON-EPILEPTIC MOVEMENTS:

Jitteriness, although not a type of seizure, is a movement disorder that is often confused with seizure. It is classically a disorder of the newborn. Jitteriness is characterized by movements primarily of tremulousness. Distinguishing jitteriness from seizure (Table:1) can be done at the bedside, by comparing the following five points.

Table-1: Difference between jitteriness and seizures in neonates

S. No	Clinical features		
1.	Abnormality of gaze or eye movement	0	+
2.	Movements, exquisitely stimulus sensitive	+	0
3.	Predominant movement	Tremor	Clonic jerking
4.	Movements cease with passive flexion	+	0
5.	Autonomic changes	0	+

The most consistently defined causes of jitteriness are HIE, hypocalcemia, hypoglycemia and drug withdrawal. It should be noted that the distinguishing clinical features described above are useful in the clinical distinction of episodic movements other than jitteriness that might be confused with an epileptic seizure.

Of particular importance is the increase of non-epileptic movements with sensory stimulation, their suppression with gentle restraint and their lack of accompaniment by metabolic changes. Finally it is important to recognize that newborns exhibit normal motor activity that could be mistaken for seizure. Awareness of such normal activity should allow ready distinction from seizure at bedside[37].

ACTIVITIES THAT ARE COMMONLY MISTAKEN FOR SEIZURES:

Awake or Drowsy:

- Roving, sometimes dysconjugate eye movements.
- Sucking, puckering movements not associated by ocular phenomenon.

Sleep:

- Fragmentary myoclonic jerk
- Isolated, generalized myoclonic jerk as infant wakes from sleep.

Of all the seizures in neonates, subtle seizure is the commonest in majority of the studies. In a study of neonatal seizures by Brunquell Philip J et al[38] subtle seizures were the commonest seen in 51% (27 out of 53), followed by focal clonic seen in 42%(22 out of53), multifocal clonic seen in 30%(16 out of 53) and generalized tonic in 23%(12 out of 53).

In a study by Lakra Mahaveer et al [39]subtle seizures were the commonest seen in 52 out of 93 cases (56.98%) followed by focal clonic seen in 21 out of 93 cases(23%) and multifocal clonic seen in 18 out of 93 cases (19.35%).

The etiology of neonatal seizures due to a combination of abnormalities is more common in sick neonates[40]. Although asphyxia is a cause of neonatal includes hypoxic-ischemic-encephalopathy (commonest cause), intracranial haemorrhage hypoglycaemia, hypocalcaemia, hypomagnesaemia, intracranial infections, developmental defects and drugs withdrawal[41]

PATHOPHYSIOLOGY:

During seizures there occurs abnormal synchronous electrical discharge (depolarization) in neuronal groups of brain. Depolarization is due to influx of sodium ions into neuronal cells, and repolarisation is due to potassium ions as they are pumped out of the cell. So the electrical potential is maintained across the cell membrane.

The electrical difference across the cell membrane is maintained mainly by the sodium potassium pump. The Na/K Pump requires ATP for its action across the membrane. This excessive depolarization of cell membrane is final common pathway of all cause of seizure.

In Hypoxia ischemia, due to energy failure, lack of ATP the Na/K ATPase pump fails which leads to alteration in the electrical potential across the membrane leading to excessive depolarization and seizures.

The mechanism of causation of seizures in metabolic abnormalities like hypoglycaemia, hypocalcemia and mainly hypomagnesemia are also by alteration in the electrical potential across the cell membrane by producing Na influx and depolarization.

REASONS FOR VULNERABILITY OF NEONATES FOR SEIZURES

- In newborns the excitatory and inhibitory circuits are not well developed and the balance is shifted towards excitatory. The GABA which is primarily an inhibitory neurotransmitter in the adult brain acts like excitatory in newborns particularly in hippocampus area.

- The activation of GABA A causes depolarization and activation of sodium channels and calcium channels. This depolarization is effective enough to release the block from NMDA channels [42] and cause influx of calcium into the immature neurons. And this step is dependent on magnesium.

- Along with this , hippocampus and other neurocortical regions of neonatal brain contains higher density of NMDA receptors, so it causes enhanced excitation and prolongation of action potential in the NMDA; and sensitivity to glycine which is actually an excitatory neurotransmitter is also increased. So finally it reduces the ability of magnesium to block NMDA receptor activity[43-47]

- The development of anticonvulsant network takes long period after birth but the proconvulsant network is well developed and fully functional during birth.

- The development and maturation of postsynaptic inhibitory system, like postsynaptic GABA-B, 5-hydroxytryptamine, and adenosine[48] are delayed.

- The Presynaptic inhibition is fully operational at birth and is mediated by adenosine, GABA-delta, and other receptors. So the inhibition in the neonatal brain predominantly will be relied upon the neurotransmitter release.

- Due to the presence of large number of gap junctions in the developing brain there occurs amplification in the small imbalances in the neuronal activity leading to disorganisation of electrical activity and seizures [49-52].

- And the refractory period in newborn are shorter and it causes hyperpolarisation during the postictal phase.

The final common pathway (Fig:3) for neonatal seizures is the changes in the energy metabolism. As soon as seizure activity is initiated there occur significant changes in the brain like

1) Decline in ATP

2) Substantial increase in the levels of adenosine diphosphate (ADP)

3) Decline in the storage form of Adenosine Tri Phosphate-phosphocreatine

4) Increase in glycolysis along with concomitant increase in pyruvate, lactate and significant decrease glucose concentration in the central nervous system (CNS)

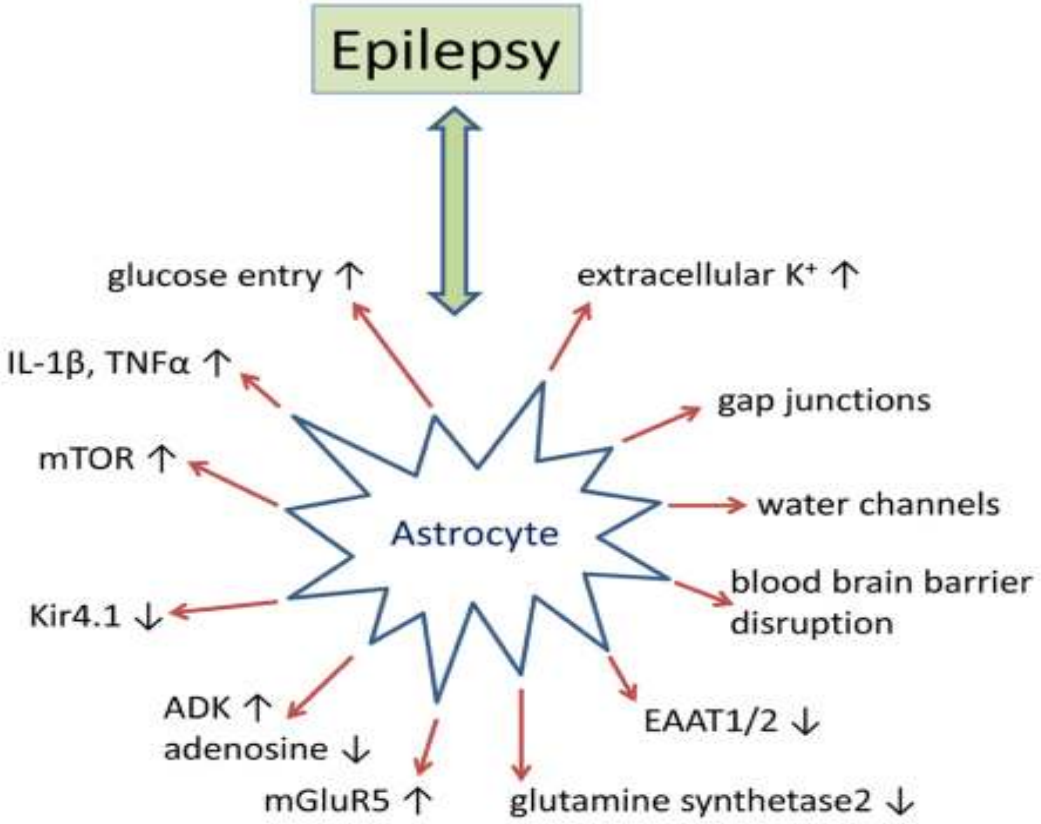


Fig 3: Pathophysiology in neonatal seizures

PATHOPHYSIOLOGICAL EVENTS IN HYPOXIC ISCHEMIC ENCEPALOPATHY:

1. Accumulation of calcium

Calcium is mainly an intracellular second messenger necessary for numerous cellular enzymatic reactions. NMDA receptor activation by hypoxic ischemic encephalopathy will cause a increase in influx of calcium into the cells. Calcium efflux across the plasma membrane is also affected by energy failure, which acts in opposite direction leading to

increased calcium inside the cells. And in addition Ca is also released into the cytoplasm from mitochondria.

All these changes in calcium homeostasis will lead to increased intracellular calcium. So the enzymatic reactions are affected leading to activation of proteases, lipases, phospholipases and endonucleases. Finally there occurs formation of free radicals as by products. It ends in persistent epiletiform discharges on electroencephalogram(Fig:4). All these abnormalities during hypoxic ischemia lead to irreversible brain damage[53]. .

2. Release of excitatory neurotransmitters:

In developing human brain glutamate is a major excitatory amino acid [54] .The action of glutamate is mediated mainly by N-Methyl-D Aspartate (NMDA) receptor and also number of receptor subtypes. And these NMDA receptors are increased in areas of active development, like striatum or hippocampus.

Within the NMDA receptor site, there are regions of antagonist activity, i.e., Magnesium ion, phencyclidine and also agonist activity, i.e., glutamate, glycine. Each of these sites has their own neuroprotective strategies.

This excessive glutamate release during hypoxic ischemic encephalopathy due to impairment in the uptake by presynaptic nerve endings will act via the NMDA receptor-mediated channel and causes intracellular entry of Calcium and leads to increased cytosolic calcium which causes irreversible brain damage.

3. Formation of free radicals

Due to hypoxic ischemic injury there is generation of free radicals like oxygen free radicals followed by nitric oxide and iron. All these free radicals act by causing injury to polyunsaturated fatty acid component [55-57]of cell membrane causing fragmentation and permanent cell death.

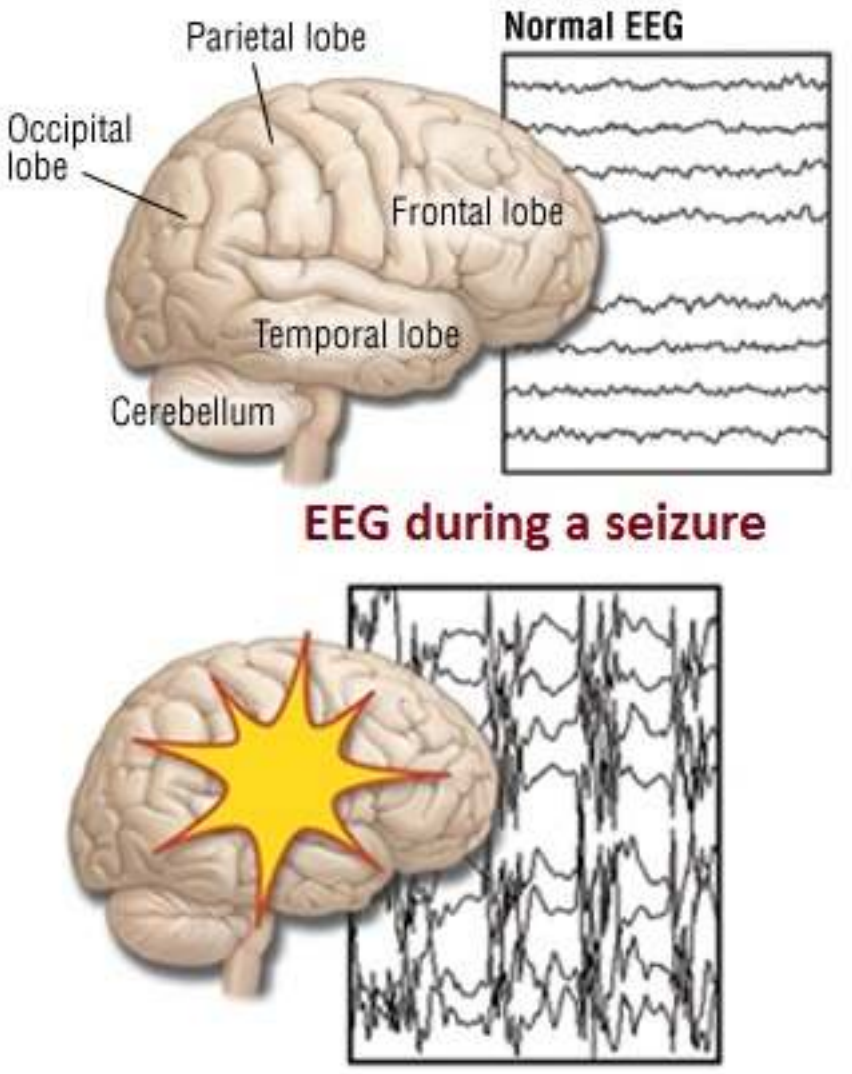


Fig: 4 EEG During seizure

ETIOLOGY OF NEONATAL SEIZURES

The cause of neonatal seizures is multiple and diverse and has evolved significantly over the last two decades. In the past, cause was undetermined in approximately one-third of infants presenting with neonatal seizures. Recent neuroimaging technology has allowed for the

detection and definition of neuropathologic changes increasing the diagnostic acumen.

In addition, improvements in neonatal intensive care have decreased mortality rates. Early onset seizures occur in HIE, ICH and metabolic causes. Late onset seizures occur with metabolic disease and drug withdrawal, but more frequently with intracranial infections[58].

The most common causes of seizures and time of onset are listed below.

I. Age 1-4 days

- Hypoxic ischaemic encephalopathy
- Drug withdrawal, maternal drug use of narcotic/barbiturates
- Drug toxicity, lidocaine, penicillin
- Intraventricular haemorrhage

Acute metabolic disorders

1. Hypocalcaemia – Perinatal asphyxia, small for gestational age, Sepsis

Maternal diabetes mellitus

Hyperthyroidism or hypoparathyroidism

2. Hypoglycaemia – Perinatal insults, Prematurity

Small for gestational age

Maternal diabetes

Hyperinsulinemic hypoglycaemia

Sepsis

3. Hypomagnesemia

4. Hyponatremia or hypernatremia

Iatrogenic/SIADH

Inborn errors of metabolism

Galactosemia

Hyperglycaemia

Urea cycle disorders

Pyridoxine deficiency (must be considered at any age)

II. Ages 4-14 days

- Infection
- Meningitis, encephalitis (enteroviral, herpes simplex)
- Metabolic disorders
- Hypocalcaemia
- Hypoglycaemia
- Drug withdrawal, maternal drug use narcotic/barbiturates
- Benign neonatal convulsions, familial and non-familial
- Kernicterus, hyperbilirubinemia

III. Ages 2-8 weeks

- Infection
- Herpes simplex or enteroviral encephalitis
- Bacterial meningitis
- Head injury – Subdural hematoma, child abuse
- Inherited disorders of metabolism
- Amino acidurias, urea cycle defects
- Organic acidurias, neonatal adrenoleucodystrophy

- Malformations of cortical development
- Lissencephaly
- Focal cortical dysplasia
- Tuberous sclerosis
- Sturge Weber syndrome

ETIOLOGY BASED ON PATHOPHYSIOLOGY

1. Acute metabolic

- Hypoglycaemia
- Hypocalcaemia
- Hypomagnesemia
- Hyponatremia or hypernatremia
- Withdrawal syndrome association with maternal drug use
- Iatrogenic associated with inadvertent fetal administration of LA
- Rare inborn errors of metabolism (including pyindoxine responsive)

2. Cerebrovascular

- Arterial and venous ischaemic stroke
- Intracerebral hemorrhage

- Intraventricular hemorrhage
- Subdural hemorrhage
- Subarachnoid haemorrhage

3. CNS Infection

- Viral meningoencephalitis
- Intrauterine (TORCH) infection

4. Developmental

- Multiple forms of cerebral dysgenesis

5. HIE

6. Genetic syndromic disorders(Rare)

- Benign neonatal familial convulsion (Na and K channel mutations)
- Early myoclonic encephalopathy

BIOCHEMICAL DISTURBANCES:

Even with established etiology for neonatal seizures there is significant contribution to the seizure activity by the underlying biochemical abnormalities. So early recognition of associated biochemical abnormalities and appropriate treatment is essential for a better outcome.

The common metabolic abnormalities responsible for neonatal seizures are hypoglycaemia, hypocalcaemia and hypomagnesemia.[14]

Hypoglycaemia:

It is one of the commonest causes of neonatal seizures. Hypoglycaemia is more frequent in SGA neonates and infant of diabetic mother. The most critical determinant for the occurrence of neurological symptoms with neonatal hypoglycaemia[59-60] is the duration of the hypoglycaemia and the time before treatment begun. It can present as seizures, jitteriness hypotonia, apnoea and stupor.

Etiology and Risk factors

1. Increased utilisation of glucose
    a. Diabetic mothers
    b. Large for gestational age infants
    c. Erythroblastosis
    d. Insulin producing tumors
    e. After exchange transfusion
2. Decreased production/stores
    a. Prematurity
    b. IUGR

c. Inadequate caloric intake

d. Delayed onset of feeding

3. Increased utilisation and/or decreased production

a. Perinatal stress

b. Endocrine deficiency

c. Defects in carbohydrate metabolism

d. Defects in amino acid metabolism

e. Polycythemia

Hypocalcemia and hypomagnesemia will be discussed in detail.

CALCIUM AND MAGNESIUM HOMEOSTASIS:

Calcium forms the major inorganic constituent of bone along with phosphorus (P).

Magnesium composition in the body makes it second common electrolyte and fourth common cation.

. The Ca and Mg composition in circulation is less than 1% of their corresponding total content distributed in the body. But the disturbances in these minerals concentration cause a significant change in the physiology manifested as clinical symptoms and signs[61]. The body

composition is in such a way that at in all age groups calcium and magnesium occupies 99% and 60 % in the skeleton respectively.

During adaptation from intra uterine to extra uterine life, the new born infant has to face certain challenges to maintain normal mineral homeostasis and to continue the rapid growth rate.

The challenges faced are

1. In intrauterine life the fetus starts to accrete calcium and magnesium at higher rates at the end of third trimester approximately calcium 120mg/kg/day and magnesium 4mg/kg/day. This high rate of accretion is discontinued abruptly after birth.
2. The homeostasis of calcium and magnesium mainly depends on the skeletal reservoir in adults which is a least reservoir in neonates[62-65]
3. The establishment of appropriate nutrient intake needed for the mineral homeostasis will take long delay in neonates especially in preterm and sick neonates
4. Neonates are in need of higher requirement of calcium and magnesium for their skeletal growth in the first year because the approximate gain in the length of newborn in first year is 25 cm.

5. Hormone mediated mineral homeostasis is inadequate in neonates because of diminished end organ responsiveness during this period.

These challenges are faced by all neonates and a healthy new born responds and adapts physiologically but in some neonates with certain risk factors like infant of diabetic mothers, prematurity and with inheritable abnormalities in calcium channel receptors there occurs hypocalcemia and hypomagnesemia[66] .

Tissue Distribution

In intrauterine life during the last trimester after 25 weeks of gestational age most of the calcium and magnesium are accrued (80%). The approximate daily accretion rate for calcium is 2.3-2.98 mmol Ca per kilogram of fetal body weight, and for magnesium 0.1-0.14 mmol Mg per kilogram fetal body weight. The total body calcium and magnesium of a newborn infant is approximately 28gms and 0.7 gms respectively[67-69]

After birth, the distribution of calcium and magnesium in the body varies significantly. The calcium occupies almost 99% in the bones but magnesium is distributed variedly with 60% in bones and 20%(Fig:5) in the muscles and rest of the magnesium is distributed in the intracellular space of other tissues.

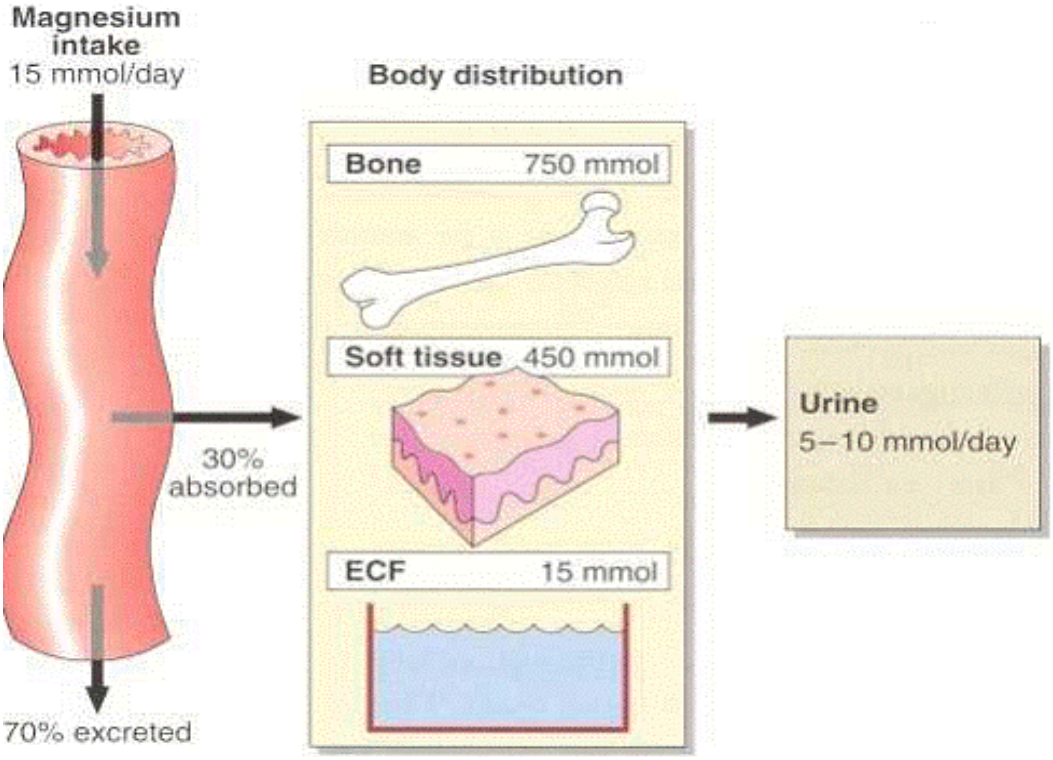


Fig 5: Distribution of magnesium

Physiologic Control of calcium and magnesium:

Hormones involved in calcium magnesium homeostasis are

1. Parathormone PTH,
2. 1,25 dihydroxyvitamin D (1,25(OH)2D)
3. Calcitonin (CT),

These hormones interact with each other and regulate the calcium and magnesium homeostasis in the body by acting on its target organs.

The chief organs response for the calcium magnesium homeostasis are : kidney, intestine and bone.

The mineral homeostasis is not only dependent on the hormonal action but a significant proportion of homeostasis is achieved by the dietary intake of the minerals calcium, magnesium, phosphorus and also on sodium, glucose and proteins.

The hormonal homeostatic mechanism for magnesium under normal physiological conditions is limited

But for the proper calcium homeostasis magnesium plays a important role because of the following reasons

- The production of parathormone hormone is regulated by magnesium and magnesium is essential for the target organ sensitivity to parathormone[70]

- For the production of active vitamin D , Mg acts as a cofactor at the step involving 25-OH VitD 1α hydroxylase enzyme

Parathyroid hormone

The chief cells of parathyroid gland secrete the hormone and it is stored in the secretory granules. The hormone increases physiologically in coincidence with the fall in serum calcium levels in new born. The main action of PTH is to increase the serum calcium levels by its action on the target organs.[71-74]

Parathormone acts directly mainly on bone and kidney, and indirectly on intestine leading to increase in serum calcium levels(Fig:6)

1. Action in bones – PTH causes of mobilisation of calcium from bones into blood by inducing the osteclasts mediated resorption in the bone
2. Action in kidneys –PTH acts by increasing the renal distal tubular reabsorption of Ca
3. Action in intestines – PTH increases the1,25(OH)2D production and secondary to this there occurs increase in intestinal Ca absorption. Action on the intestine is dependent on vitamin D

Decrease in the serum levels of magnesium stimulates PTH secretion,[75-76] but chronic hypomagnesemia usually causes inhibition of secretions of PTH.

Mg is needed for adenylate cyclase, which gets inactivated during hypomagnesemia**.** This is the reason why there is increased resistance to action of PTH due to hypomagnesemia.

Calcitonin

It is secreted primarily by the C cells of parathyroid gland and significant contribution from other tissues like mammary gland, brain pituitary and placenta. Its secretion initially increases in immediate

postnatal life and reaches a level 10 times higher than in the adults. Then calcitonin levels decrease steadily during infancy.

The increase in serum calcium and serum magnesium concentration increases the serum calcitonin levels mediated through gastrin, glucagon and cholecystokinin.

Hypocalcaemia, and vitamin D, suppresses the secretion of calcium. Calcitonin cats by increasing the renal excretion of phosphorus, Mg, and sodium. So it decreases the serum calcium concentration and it acts opposite to the action of PTH.

Vitamin D

Vitamin D is usually obtained from diet and also synthesized endogenously. Dietary vitamin D is derived from plant sources in the form of ergocalciferal (vitamin D2) and from animal sources[77] in the form of cholecalciferal (vitamin D3).

- Vitamin D is carried in the circulation by carrier protein and albumin

- After its absorption into the liver it gets hydroxylated at the carbon 25 end to 25-OHD.

- Normally in body the most abundant form of vitamin D is 25-OHD

- Final step in the activation of vitamin occurs at the level of kidneys by its action on 25-OHD. It is hydroxylated further to 1,25(OH)2D by 25-OHD-1αhydroxylase and to 24,25-dihydroxy vitamin D by 25-OHD-24 hydroxylase.

Non-classic control of mineral homeostasis

Factors controlling these mineral homeostasis other than major hormones are insulin-like growth factor I, cortisol, estrogen, progesterone, TNF, transforming growth factor-β1, IL-1, IL-2,4&6, TNF-α and interferon V. All these play a inter role in calcium and magnesium homeostasis.

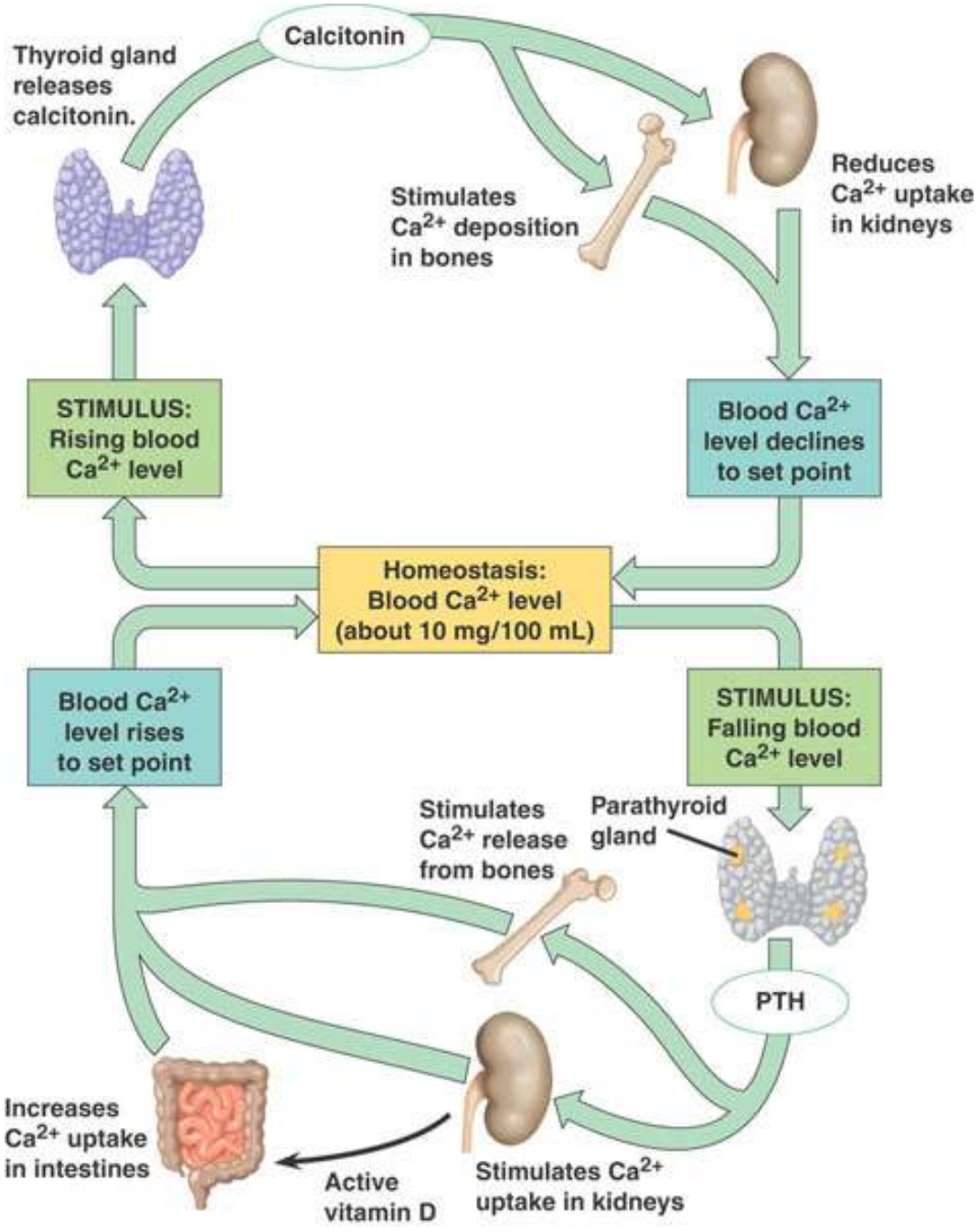


Fig 6: Calcium Homeostasis

Hypocalcemia

Hypocalcemia in newborn is defined by total calcium serum concentration in term infants less than 2 mmol/L (8 mg/dL) and 1.75 mmol/L (7 mg/dL) in preterm infants. And for measurement of iCa hypocalcemia is defined as levels below 1.0 to 1.1 mmol/L (4.0 to 4.4 mg/dL) depending on the particular ion-selective electrode used.[78]

Hypocalcemia is classified into two types

1. Early onset hypocalcemia- it occurs classically within first 72 hours of life. Classically associated with prematurity, IUGR, Asphyxia and gestational diabetes.

2. Late onset hypocalcaemia –which occurs after 72 hours of life mainly during end of first week.

Risk factors for hypocalcaemia

Maternal

- Insulin dependent diabetes
- Hyperparathyroidism
- Vit D or magnesium deficiency
- Medications: Calcium antacid and anticonvulsant

Peripartum: Birth Asphyxia

Infant

- Intrinsic Prematurity
- Malabsorption
- Malignant infantile osteopetrosis
- Parathyroid hormone: impaired synthesis, secretion, regulation or responsiveness.
- Extrinsic Diet – Adequate calcium
- Excess phosphorus
- Enema – phosphate
- Exchange transfusion with citrated blood

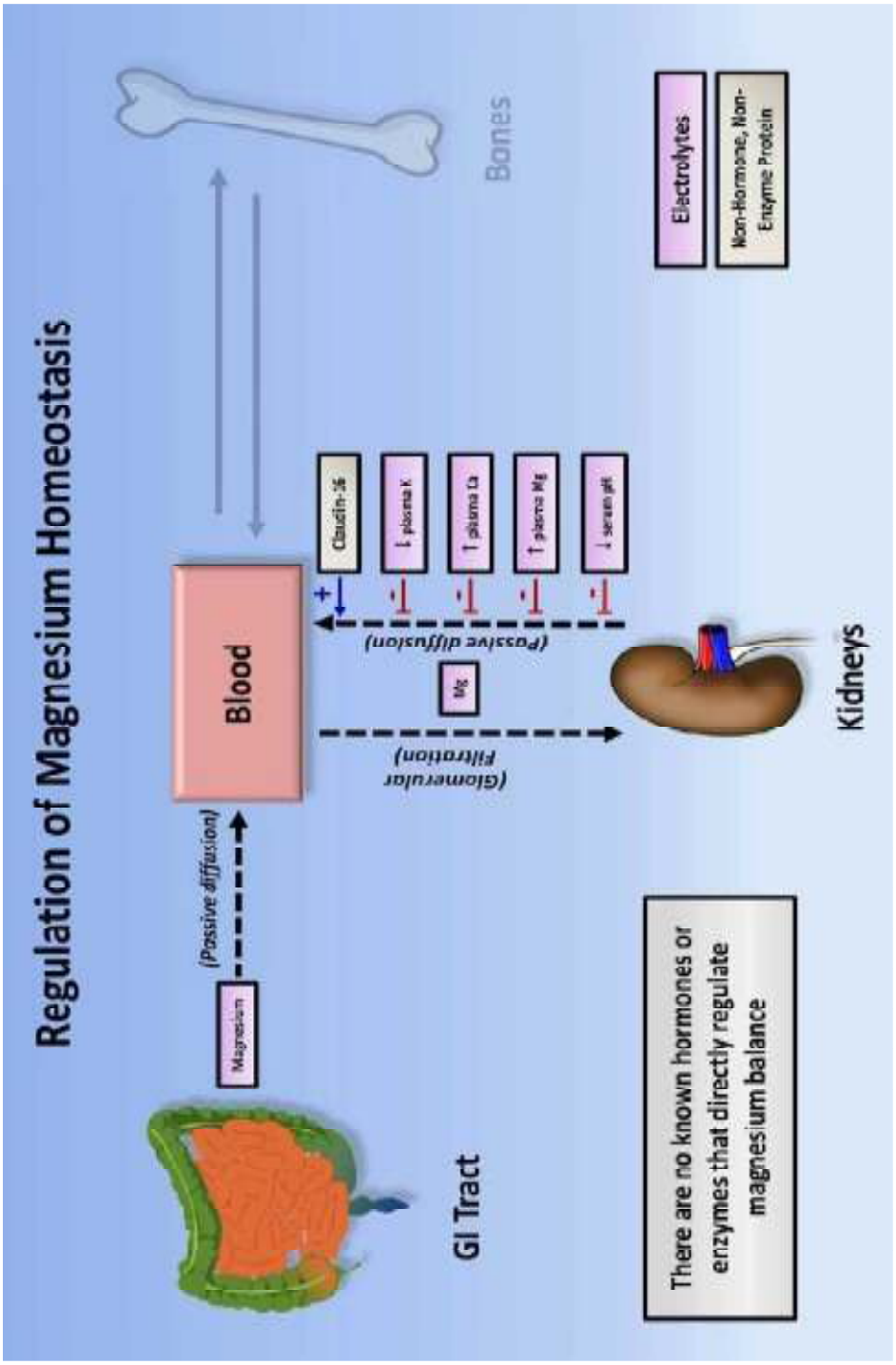
Hypomagnesemia

The normal serum magnesium concentration is 0.7 – 1.15 mmol/l (1.7-2.8mg/dl). In body the majority distribution of magnesium is in the intracellular compartment that is around 90% , so hypomagnesemia indicates the decrease in total magnesium levels in the body, but plasma levels of magnesium can be normal.

Magnesium acts on the Na/K ATPase pump in the cell membrane and maintains the electrical potential gradient across the cell membrane and also maintains normal potassium concentration. So hypomagnesemia causes disturbances in this electrical gradient leading to excitability of cells.

Regulation of magnesium levels are not influenced by hormones or enzymes directly (Fig: 7)

Fig 7: Magnesium homeostasis



Causes of neonatal hypomagnesemia

1. Decreased tissue accretion
    - Infants of mothers with insulin-dependent diabetes or hyperparathyroidism
    - Small for gestational age infants
    - Chronic maternal magnesium deficiency
2. Decreased absorption
    - Extensive small intestine resection
    - Specific intestinal magnesium malabsorption
3. Increased loss
    - Intestinal fistula or diarrhoea
    - Hepatobiliary disorders
4. Decreased renal tubular reabsorption
    - Primary – transient receptor potential channel protein mutation, renal tubulopathies with hypo or hypercalciuria
    - Secondary – extracellular fluid compartment expansion, osmotic diuresis, drugs (e.g.: loop diuretic, aminoglycoside, ibuprofen ovedose).

5. Others

   - Increased phosphate intake
   - Exchange transfusion with citrated blood

6. Inherited disorders of renal magnesium handling

   - Primary hypomagnesemia with secondary hypocalcemia
   - Infantile isolated renal magnesium wasting (dominant)
   - Infantile isolated renal magnesium wasting (recessive)
   - Hypomagnesemia with hypercalciuria and nephrocalcinosis

All these inheritable forms are due to mutation in the various proteins like transient receptor potential melastatin type 6(TRPM6), Cyclin M2(CNNM2), Claudin [79-80].

CLINICAL FEATURES OF HYPOMAGNESEMIA:

Early Symptoms

- Anorexia,
- Nausea,
- Muscular weakness,
- Cramps,
- Lethargy and weight loss .

Late Symptoms

- Hyperirritability,
- Hyper excitability,
- Muscle spasms,
- Stridor
- Tetany,
- Convulsions.
- Hypertension is common and pulmonary oedema can occur.
- Supraventricular and ventricular tachyarrhythmia's may also occur.

TREATMENT OF HYPOMAGNESEMIA

Hypomagnesemia if identified should not be treated alone with calcium or vitamin D because it will further aggravates the decrease in serum magnesium levels leading to worsening of symptoms.

The treatment of hypomagnesemia is using magnesium salts. The dose of IV magnesium in the neonate is a 50% solution of magnesium sulfate, 0.05 to 0.1 mL/kg (0.1 to 0.2 mmol/kg, or 2.5 to 5.0 mg/kg of elemental magnesium). It has to be given either as slow intravenous

infusion or intramuscularly .based on the clinical response we need to repeat doses every 8 to 12 hours.

MECHANISM OF ACTION OF MAGNESIUM SULPHATE :

The anti epileptogenic property of magnesium sulphate is due to its following actions

1. Effects of magnesium sulphate on blood
2. Effect of magnesium sulphate on blood brain barrier
3. Effect on NMDA channels in brain

EFFECTS OF MAGNESIUM SULPHATE ON BLOOD VESSELS

Magnesium acts as good vasodilator of uterine arteries, aorta ,and mesenteric arteries but on cerebral arteries the vasodilator effects are minimal.

Decreased intracellular calcium, causes relaxation and vasodilatation. In endothelium, magnesium by unknown mechanism increase production of prostaglandin I2, which also decreases platelet aggregation. By increasing NO magnesium causes vasodilatation (Figure 8).

Vascular Effects of Magnesium Sulfate.

Cellular Target	Mode of Action	Possible Mechanism(s)
Smooth Muscle Uterine +++ Mesenteric +++ Aorta +++ Cerebral +	Relaxation ↓ Vasodilation ↓ Decreased Vascular Resistance	Calcium Antagonism Decreased Voltage-operated Calcium Channel (VOCC) Activity Decreased $[Ca^{+2}]_i$ Release From Sarcoplasmic Reticulum
Endothelium	Decreased Platelet Aggregation	Increased Prostaglandin I_2 (PGI_2)
	Vasodilation	Increased Nitric Oxide (NO, Gestation Dependent)

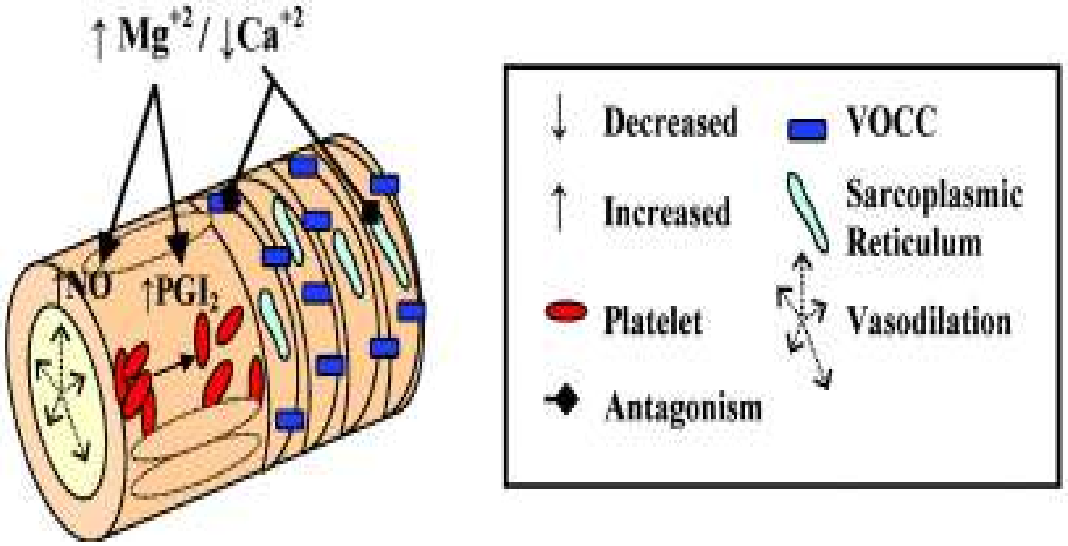


Fig 8: Effects of magnesium sulphate on blood vessels

EFFECT OF MAGNESIUM SULPHATE ON BLOOD BRAIN BARRIER

Magnesium decreases the cerebral edema by its calcium antagonistic effect. Decreased cellular calcium leads to decreased endothelial cell contraction so preventing opening of tight junctions.

1. This inhibits the paracellular transport of vascular contents, proteins, and ions. So the paracellular transport of contents causing edema is prevented by the action of magnesium.

2. Magnesium also acts by down regulating the aquaporin 4 (AQP4), situated at astrocytic end feet. By its down regulation it decreases cerebral edema. (through unknown mechanisms) (Figure 9).

Effect of Magnesium Sulfate on Cerebral Edema and the Blood-brain Barrier.

Cellular Target	Mode of Action	Possible Mechanism
Cerebral Endothelium	Decreased Blood-brain Barrier (BBB) disruption ↓ Limited Cerebral Edema Formation Via Paracellular Transport	Calcium Antagonism ↓ Decreased Cell Contraction ↓ Decreased Tight Junction Permeability
	Limited Transcellular Transport	Decreased Pinocytosis
Astrocyte	Limited Cerebral Edema	Decreased Aquaporin 4 (AQP4) Expression

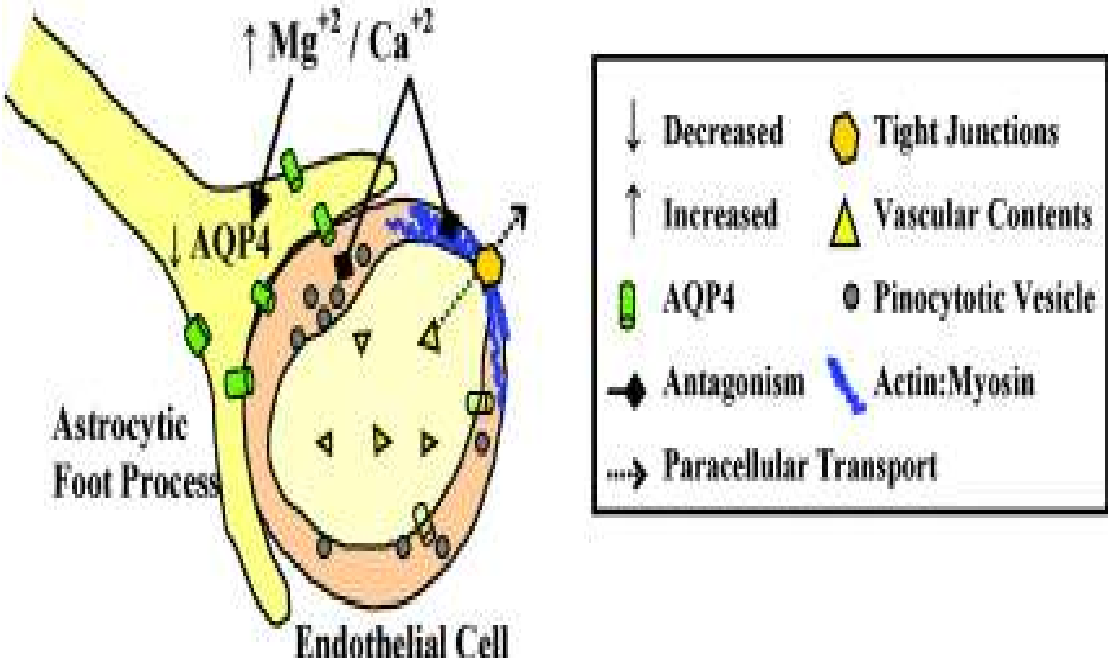


Fig : 9 Effect of magnesium sulphate on blood brain barrier

ANTICONVULSANT ACTIVITY OF MAGNESIUM SULPHATE

There is mass release of excitotoxic neurotransmitters including glutamate during seizures. This excess glutamate activate NMDA receptor, causing depolarization of numerous neurons. Magnesium by inhibiting NMDA receptors increase the seizure threshold, and limits the effect of glutamate.

Anticonvulsant Activity of Magnesium Sulfate.

Cellular Target	Mode of Action	Possible Mechanism
Neurons	Increased Seizure Threshold	N-Methyl-D-Aspartate (NMDA) Receptor Antagonism ↓ Decreased Effect of Glutamate, Limiting Massive Neuronal Depolarization

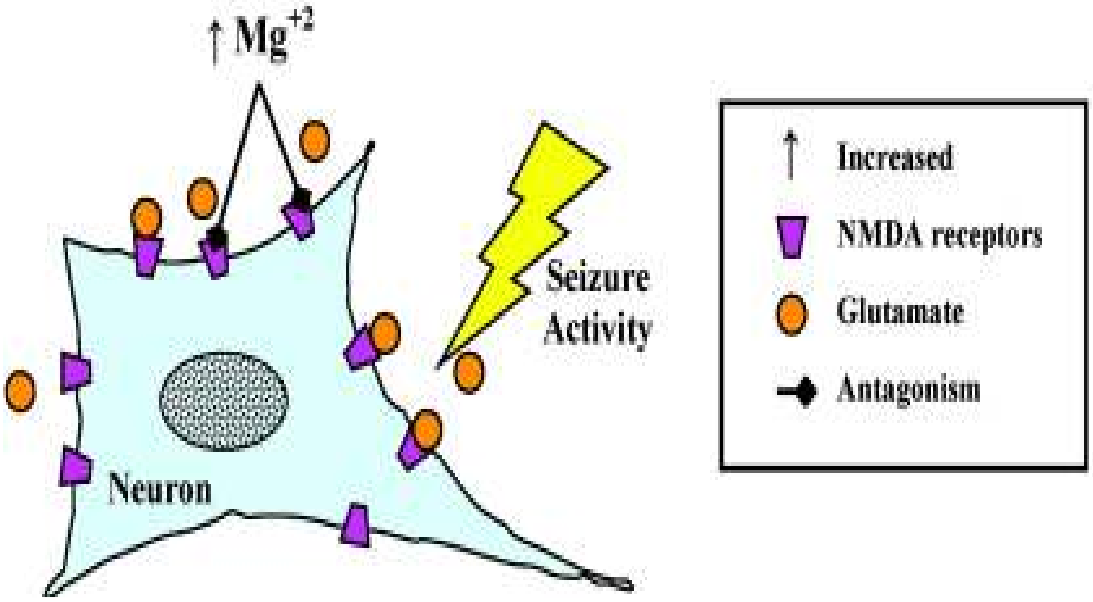


Fig 9: Anticonvulsant activity of magnesium sulphate

METHODOLOGY

METHODS OF COLLECTION OF DATA

The present study is an observational study included 150 neonates presenting with seizures admitted to NICU of Coimbatore medical college, hospital , Coimbatore during the period of one year from July 2014 to July 2015.

INCLUSION CRITERIA

1. Neonatal seizures occurring in the first 4 weeks of life
2. Neonates with neonatal seizures who were delivered at our hospital as well as outborn babies are included in the study.
3. Neonates presenting with at least one of the following clinical type of seizures
    - Subtle seizures
    - Generalised tonic seizures
    - Multifocal clonic seizures
    - Focal seizures
    - Myoclonic seizures

EXCLUSION CRITERIA

1. Jitteriness in neonates.
2. Tetanic spasms in neonates.
3. Outborn neonates treated with anticonvulsants were excluded from the study.
4. Infant of diabetic mother
5. Newborn with Congenital anomalies like Hydrocephalus, Arnold Chiari malformation, Dandy Walker malformation.

Seizure:

Seizure is defined as paroxysmal involuntary disturbance of brain function that may manifest as an impairment or loss of consciousness, abnormal motor activity, behavioral abnormality, sensory disturbance or autonomic dysfunction.

Neonatal Seizures:

Seizures occurring during first 4 weeks of life classified as neonatal seizures.

These are classified according to classification given by Hill and Volpe in 1994.[1]

After selection of study group the predesigned proforma has been filled and the following histories are recorded

Antenatal history

- Age and parity of mother were noted.
- History of whether regular ANC checkups were done or not was enquired
- History of medical illness like diabetes, fever during pregnancy were asked.
- History of obstetric complications like PIH, eclampsia, antepartum hemorrhage, oligo or polyhydromnios were taken
- History regarding medication enquired.

Perinatal history

- History of PROM,
- Prolonged second stage of labour,
- Meconium staining of liquor,
- Place of delivery, type of delivery
- Indication for forceps and caesarean section were enquired.
- After delivery whether baby cried immediately or not,

- Any resuscitation done, were enquired.
- If apgar score was done, it was noted
- Medication given to the baby were recorded.

Definition of birth asphyxia : The neonate was diagnosed with birth asphyxia if baby did not cry for more than three minutes after birth or documented apgar score was ≤ 3 at one minute and < 7 at 5 minutes of birth.

Postnatal history

- History of lethargy poor feeding,
- History of jaundice,
- History of excessive cry,
- History of fever, vomiting
- History of seizures were taken.

History of seizures

Clinical details of each seizure is recorded in following pattern

- Age of onset of seizures,
- Type of seizures,
- The duration of seizures,

- Number of seizures and
- Consciousness during and between seizures were taken.

The neonatal seizures were-classified according to Volpe's classification into multifocal, clonic, focal tonic, tonic-and myoclonic.

After appropriate history, detailed examination of neonate was done.

Examination

The vitals of the baby were recorded

- Heart Rate,
- Respiratory Rate,
- Peripheral pulses,
- Blood pressure,
- Temperature,
- Capillary filling time
- General physical examination of neonate was done according to the proforma and any disparity in head size and shape, skin lesions were noted.

- Anthropometry of the neonate was recorded and gestational age was assessed according to New Ballard Scoring.

- CNS examination was done as per the proforma. Other systems were also examined.

Investigations

The following investigations were done for neonatal seizures in all cases.

1. Complete blood counts (hemoglobin, total count, differential count). Using sysmex Auto Analyser (Fig : 11)

Fig 11: Sysmex auto analyzer

2. Sepsis screening:

Peripheral smear for band cells and toxic granules,

C-Reactive Protein

Blood culture if necessary.

3. Blood glucose:

Random blood sugar was done urgently with glucostick and then confirmed by glucose oxidase method.

Hypoglycaemia was diagnosed if RBS is <40 mg/dL.

4. Serum electrolytes were done on emergency basis,

- S. Ca, S. Na, S. Mg were done
- Hypocalcaemia was defined when total serum calcium <7.0 mg/dL,
- Hypomagnesemia when serum Mg < 1.5 mg/dL,
- Hyponatremia when S. Na <135 meq/L and
- Serum calcium estimation by O-Cresolphthalein Complexone (OCPC) method.
- Serum sodium and potassium estimation by I.S.E. Method (Ion Selective electrode)

- Blood Glucose estimation by Glucose oxidase method.
- Serum magnesium by Arsenazo dye binding method

In selected cases

1. **CSF Analysis:** If septicemia or meningitis was suspected. LP was done and CSF analysed for.
    - Cytology – Cell type, cell count
    - Biochemistry – Glucose, protein, Chloride.
    - Micro Biology – Culture, Gram Staining
    - Neonatal meningitis was diagnosed if CSF culture showed growth of organisms.

Fig 12:CSF analysis

2. Chest X-ray was done in required cases
3. USG examination was done in all babies with neonatal seizures to rule out ICH, hydrocephalus, congenital anomalies of brain and infarction.
4. EEG Done whenever indicated to find out etiology
5. CT-scan brain
6. Other metabolic screening like serum ammonia was done if particular metabolic disease was suspected.

All the patients were treated according to the protocol and diagnosis made.

The results obtained were tabulated in the master chart and by applying the statistical analysis results were obtained.

STATISTICAL ANALYSIS:

Statistical analysis was performed using the Statistical software package [SPSS, version16.0 for windows] and consisted in computing the frequency count and percentages for qualitative variables, the mean and standard deviation for quantitative variables.

The comparison of the percentages and the means were performed using the chi-square test and the unpaired Student t-test p-value <0.05 was considered significant.

Sample Size Calculation formula

$$n = \frac{t^2 \text{ x } p\ (1 - p)}{m^2}$$

Description:

n = required sample size

t = confidence level of 95%

p = Expected Frequency of the Factor under Study – 10%

M = margin of error of 5%

$$n = \frac{1.96^2 2\text{x } 0.10\ (1 - 0.10)}{.05^2}$$

= 138

Contingency

The sample is further increased by 10% to account for contingencies such as non-response or recording error.

n +10 % = 138 + 10% =**152Samples**

150 Samples (Round off)

OBSERVATION AND ANALYSIS

1. PREVALANCE OF HYPOMAGNESEMIA IN THE STUDY GROUP

Among the 150 study group hypomagnesemia is detected in 7 babies which are around 4.6% of the group.

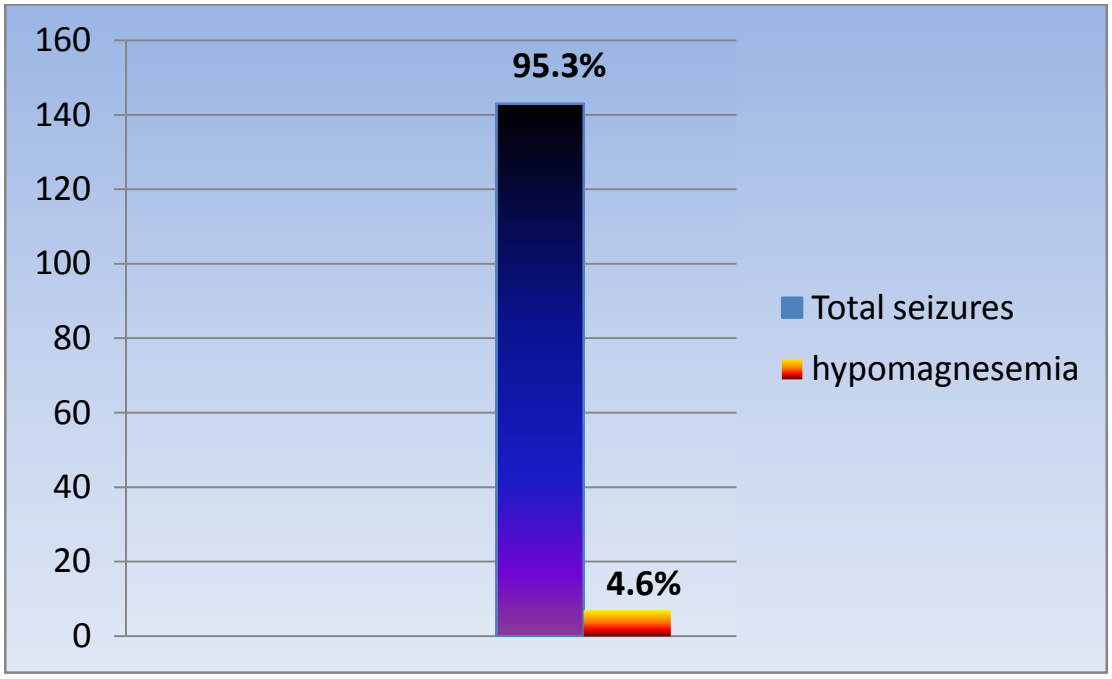


Fig 13: Prevalence of hypomagnesemia in the study group

2. DISTRIBUTION OF CAUSES OF SEIZURE IN THE STUDY GROUP

Among the 150 study group hypoxic-ischemic encephalopathy is the most common cause of seizures (38.7%)

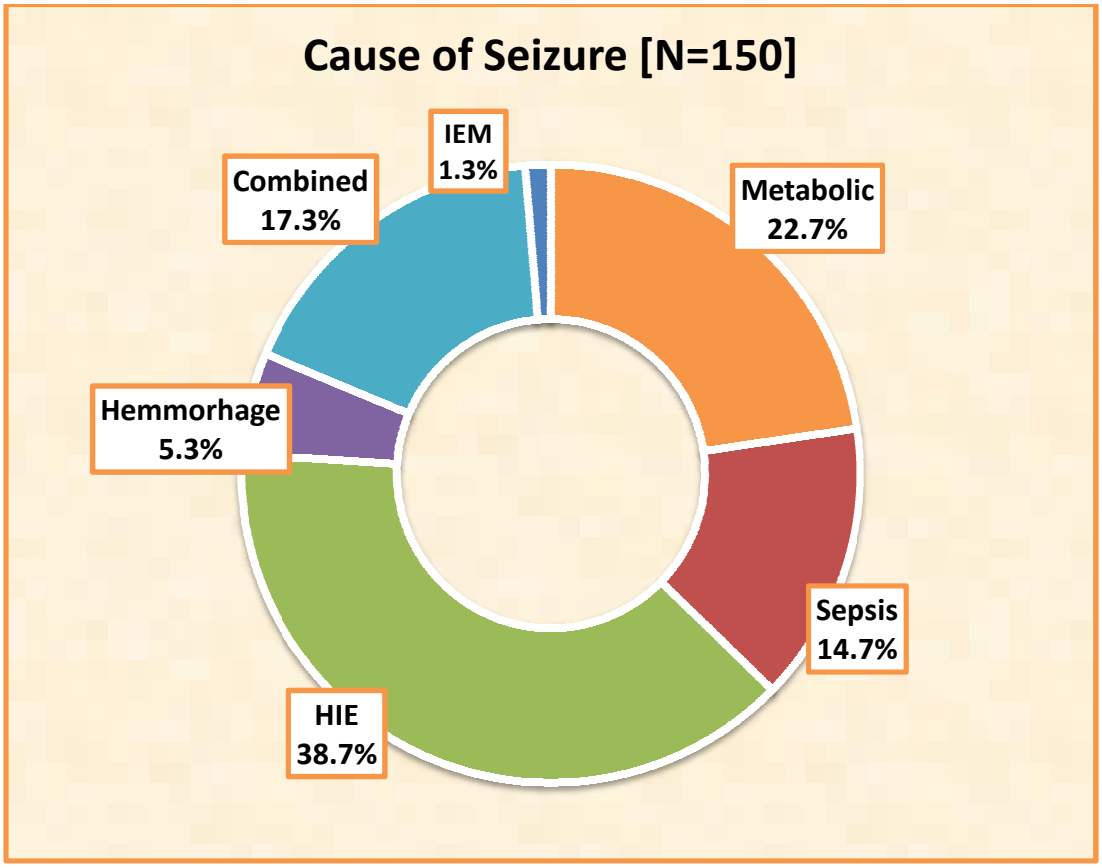


Fig 14 : Distribution of causes of seizure in the study group

Table 2 : Distribution of causes of seizures in the study group

Causes	n	(%)
Metabolic	34	22.7%
Sepsis	22	14.7%
HIE	58	38.7%
Haemorrhage	8	5.3%
Combined	26	17.3%
IEM	2	1.3%
Total	150	100%

In our study the most common cause seizure is Hypoxic ischemic encephalopathy with 38.7 % of total followed by Metabolic causes with 22.7% of total. Sepsis/Meningitis causes 14.75% and intracranial bleed with IEM occupies the least common etiology.

Significant proportion of group is occupied by combined cause which is around 17.3% mainly sepsis combined with electrolyte abnormalities.

3. DISTRIBUTION OF AGE AND GENDER IN THE STUDY GROUP

Among the study group most of the seizures occurs around the age group of < 5 days and male preponderance.

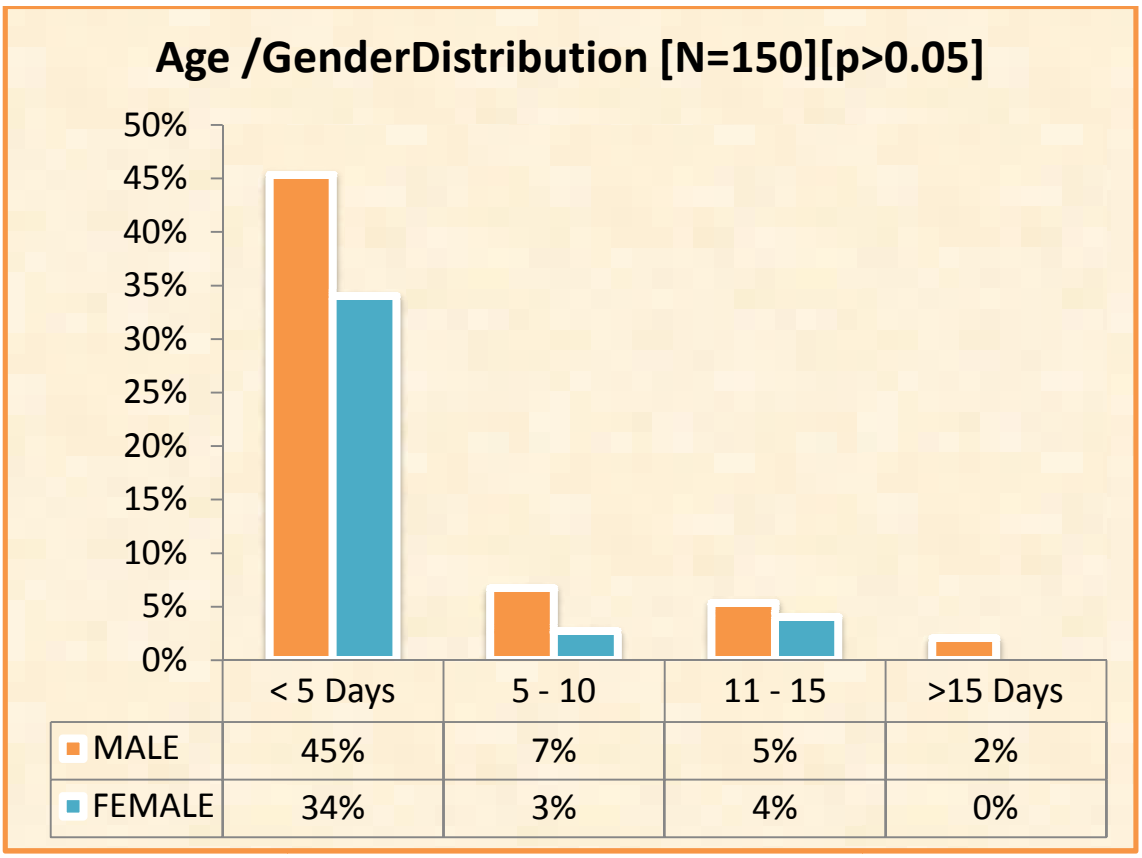


Fig 15 : Distribution of age and gender in the study group

Seizures in <5 days age group occupies 79%, 5-10 days age group and 11-15 days age group occupies 10% and 9% respectively.

4. DISTRIBUTION OF GENDER IN THE STUDY GROUP

In the selected group during the study period there is slight male preponderance in the occurrence of seizures with males occupying 59% and female child 41% .

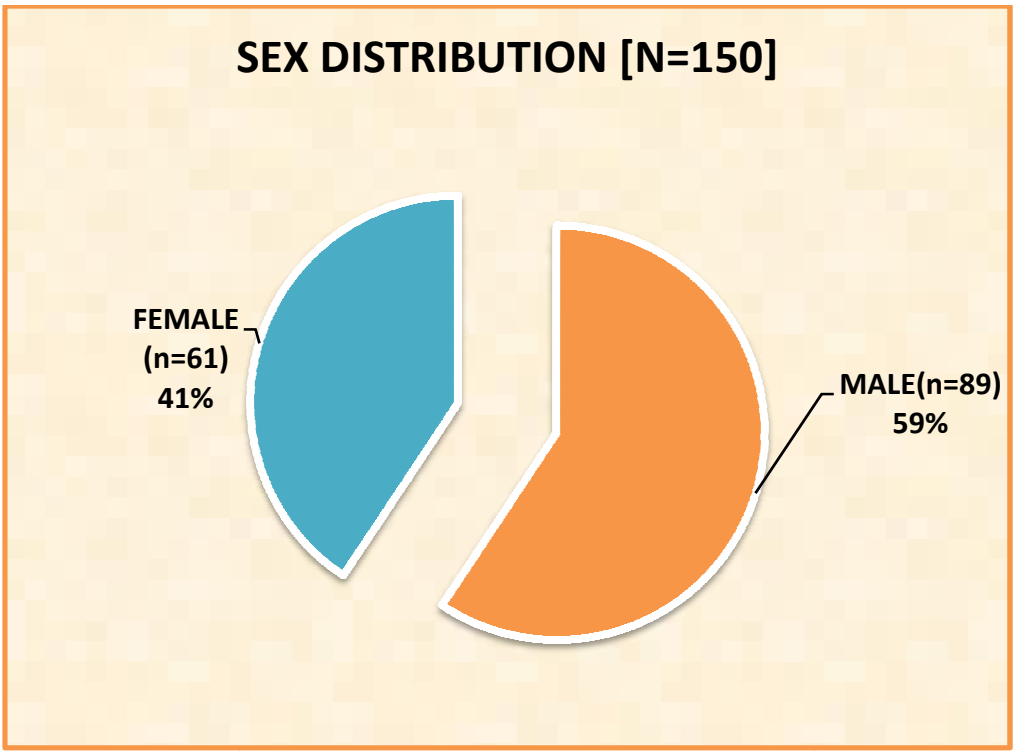


Fig 16 : Distribution of gender in the study group

5. DISTRIBUTION OF AGE IN THE STUDY GROUP:

In the selected study group most common age of seizure occurrence is in less than 5 days group which occupies 79% of the total

Table 3 : **Distribution of age in the study group**

AGE	GENDER		TOTAL	(%)
	MALE	FEMALE		
< 5 Days	68	51	119	79%
5 - 10	10	4	14	9%
11 - 15	8	6	14	9%
>15 Days	3	0	3	2%
TOTAL	89	61	150	

The seizures occurring in >15 days age group is least which is around 2% in the study group implying that neonates are vulnerable to seizures in their early neonatal period.

6. MEAN AGE OF OCCURRENCE OF SEIZURES IN THESTUDY GROUP

The mean age of occurrence of seizure among males is 4.28 days and mean age for female is 3.54 days but it is statistically insignificant.

Table 4: Mean age of occurrence of seizures in the study group

Mean Age with Gender							
	Mean		95% CI for Mean				
Gender	[Days]	SD	Lower	Upper	Minimum	Maximum	Sig
MALE	4.28	4.801	3.27	5.29	1	24	
FEMALE	3.54	3.364	2.68	4.4	1	14	>0.05
Total	3.98	4.278	3.29	4.67	1	24	

And the mean age of occurrence of seizures in the total group is 3.98 days, which in favours that the insults in earlier days are more severe and leads to long term sequale.

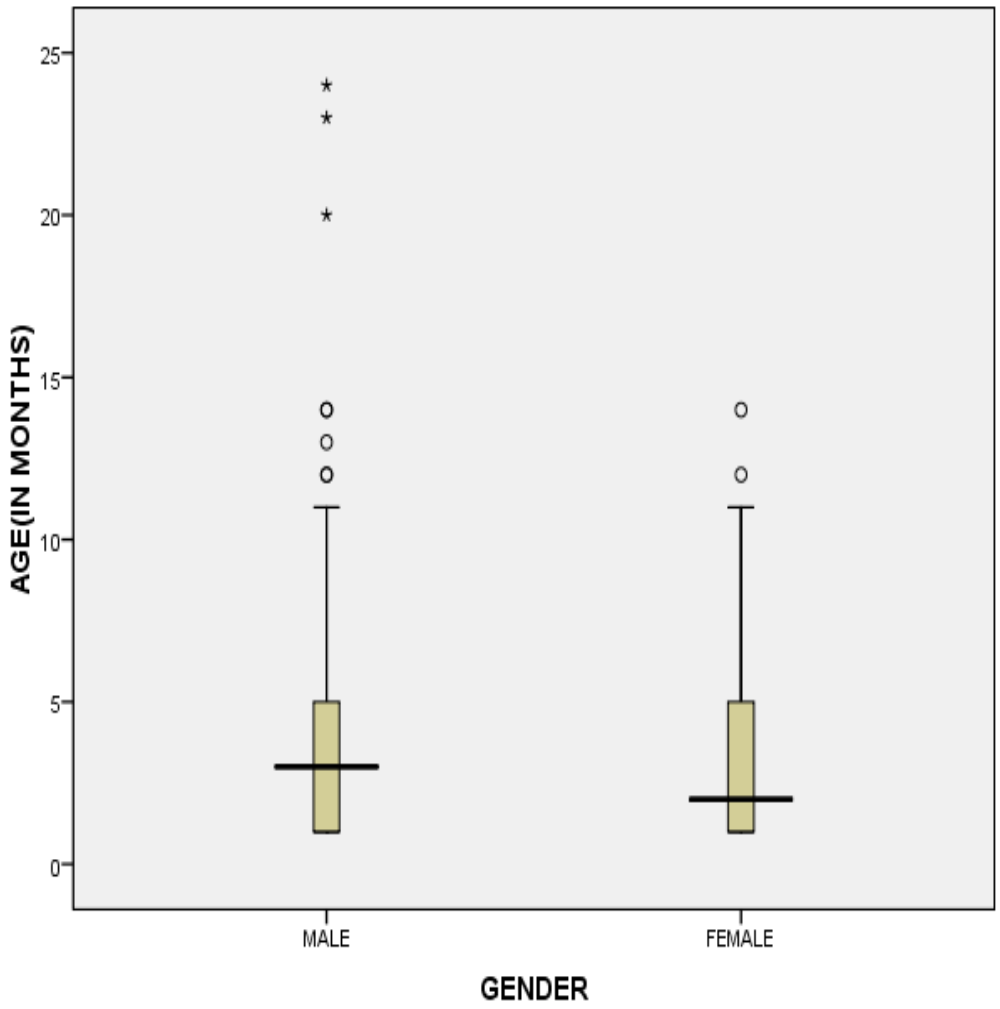


Fig 17 : Mean age of occurrence of seizures in the study group

7. DISTRIBUTION OF GESTATIONAL AGE AMONG THE STUDY GROUP

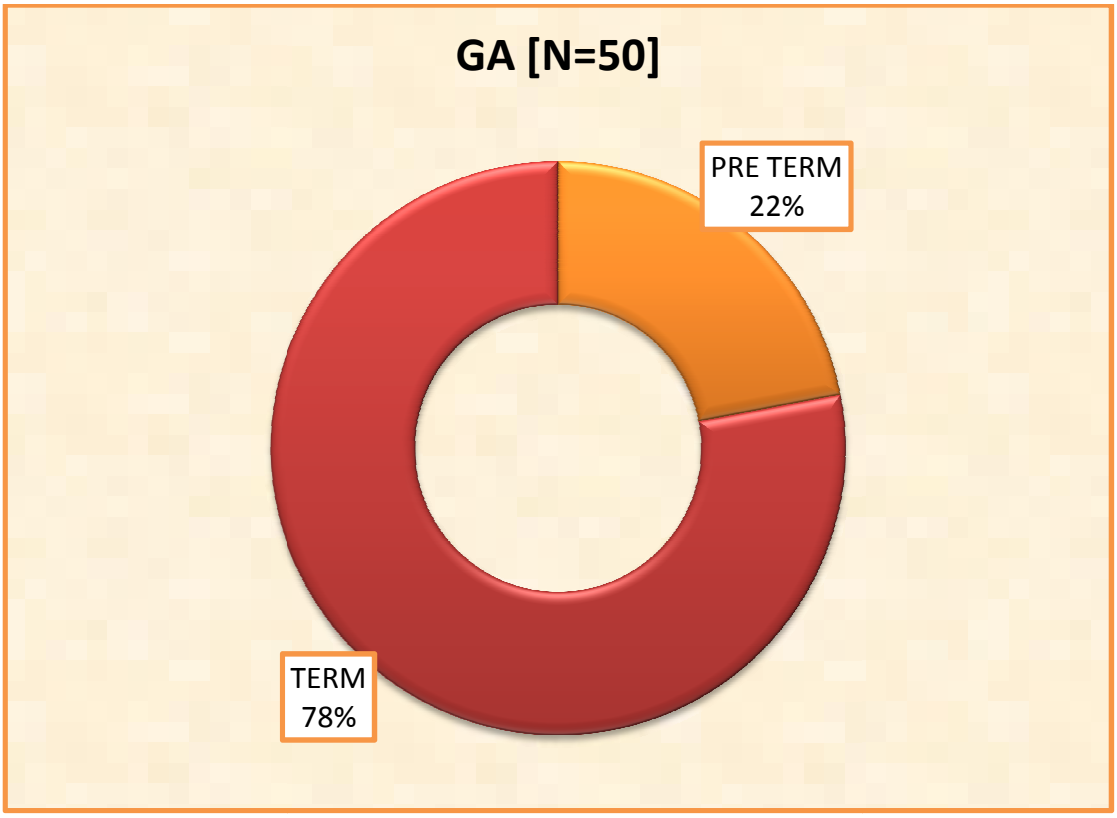


Fig 18 : Distribution of gestational age among the study group

Table 5: Distribution of gestational age among the study group

GA	n	(%)
PRE TERM	33	22%
TERM	117	78%
Total	150	100%

In the study group of 150 selected term babies occupies 78% of the total and 22% of the total is preterm babies.

8. MEAN TIME OF ONSET FOR SEIZURES IN THE STUDY GROUP

The mean time of onset of seizures in the study group is < 5days.

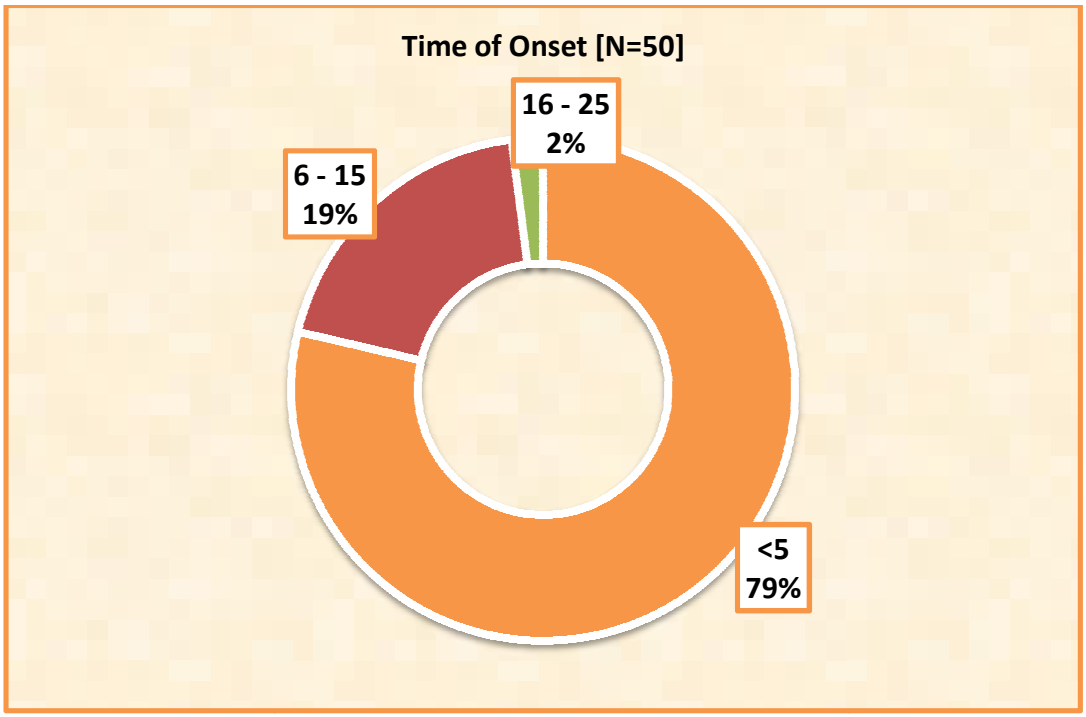


Fig 19 : Mean time of onset for seizures in the study group

Table 6 : Mean time of onset for seizures in the study group

Duration	n	(%)
<5	118	79%
6 - 15	29	19%
16 - 25	3	2%
Total	150	100%

Table 7: Mean time of onset of seizure

Mean Time of on set						
	Mean		95% CI for Mean			
Duration		SD	Lower	Upper	Minimum	Maximum
Time[Days]	4.11	4.368	3.41	4.82	1	25

The mean time of onset for neonatal seizures in the study group selected is 4.11 days.

9. DISTRIBUTION OF METABOLIC ABNORMALITY AMONG THE STUDY GROUP

Though there is an established cause for seizures metabolic abnormalities are associated in 79 cases.

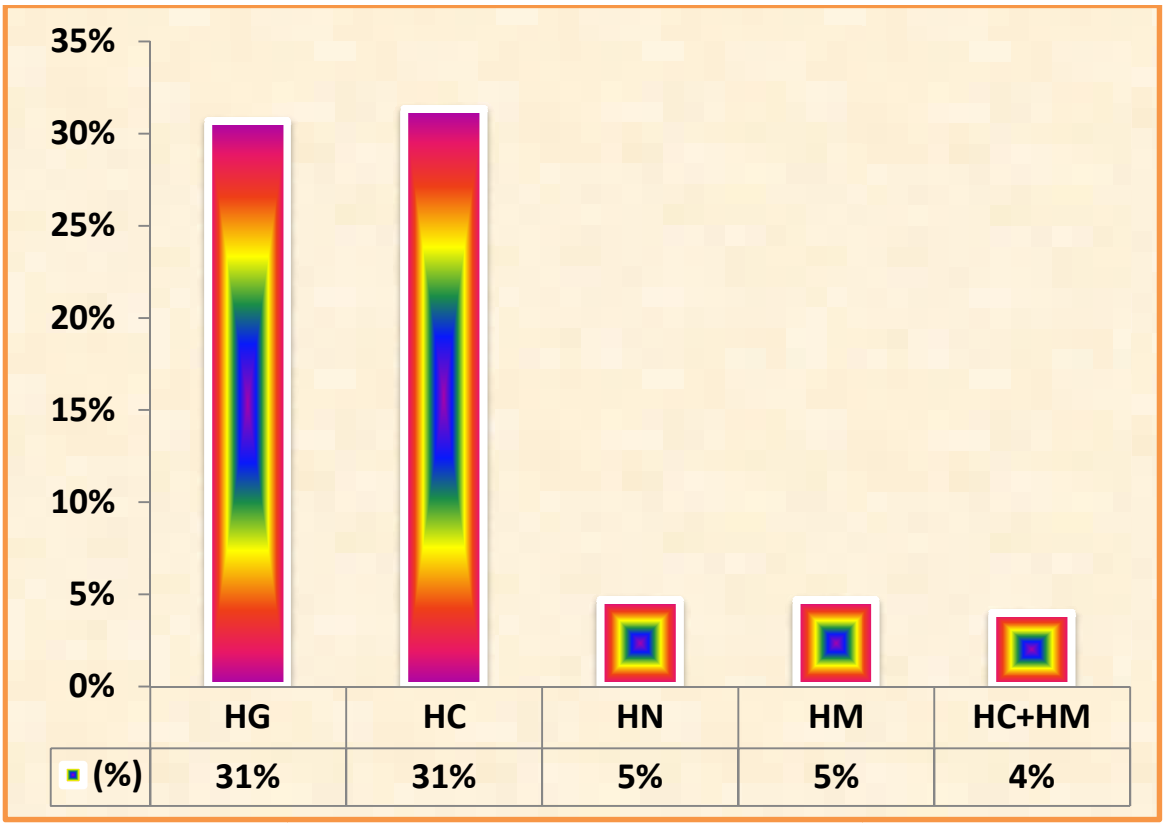


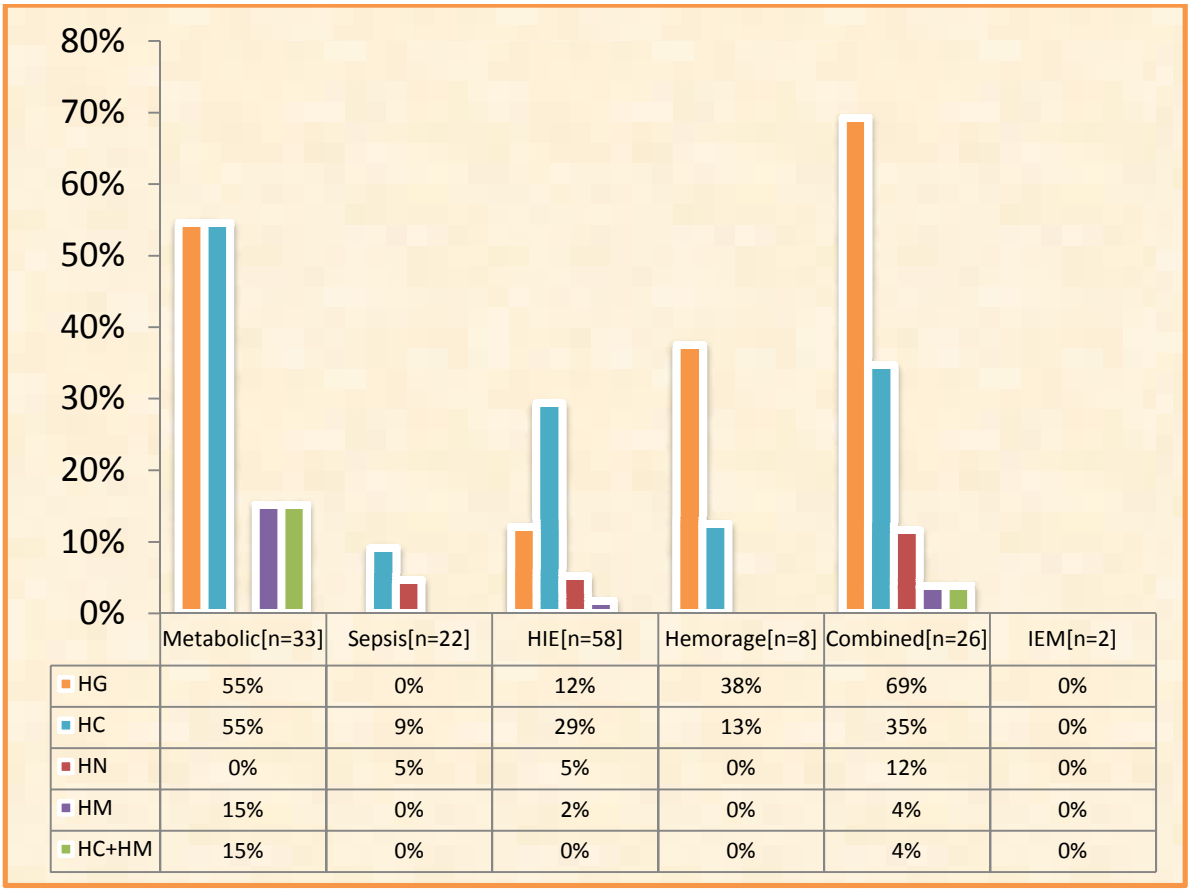
Fig 20 : Distribution of metabolic abnormality among the study group

Table 8: Distribution of metabolic abnormality among the study group

CLINICAL VARIABLES	n	(%)
Hypoglycaemia	46	30.7%
Hypocalcemia	47	31.3%
Hyponatremia	7	5%
Hypomagnesemia	7	5%
HC+HM	6	4%

So among the associated metabolic abnormality hypoglycaemia and hypocalcemia are the most common with 31% of each, followed by hyponatremia and hypomagnesemia occupying 7% each.

10. ASSOCIATION OF CAUSE OF SEIZURE WITH METABOLIC ABNORMALITY



	Metabolic[n=33]	Sepsis[n=22]	HIE[n=58]	Hemorage[n=8]	Combined[n=26]	IEM[n=2]
HG	55%	0%	12%	38%	69%	0%
HC	55%	9%	29%	13%	35%	0%
HN	0%	5%	5%	0%	12%	0%
HM	15%	0%	2%	0%	4%	0%
HC+HM	15%	0%	0%	0%	4%	0%

Fig 21 : Association of cause of seizure with metabolic abnormality

Among the selected group HIE is most commonly associated with other biochemical abnormalities that is around 28 cases out of 58 are associated with biochemical abnormalities and hypocalcemia is the most common metabolic abnormality associated with HIE

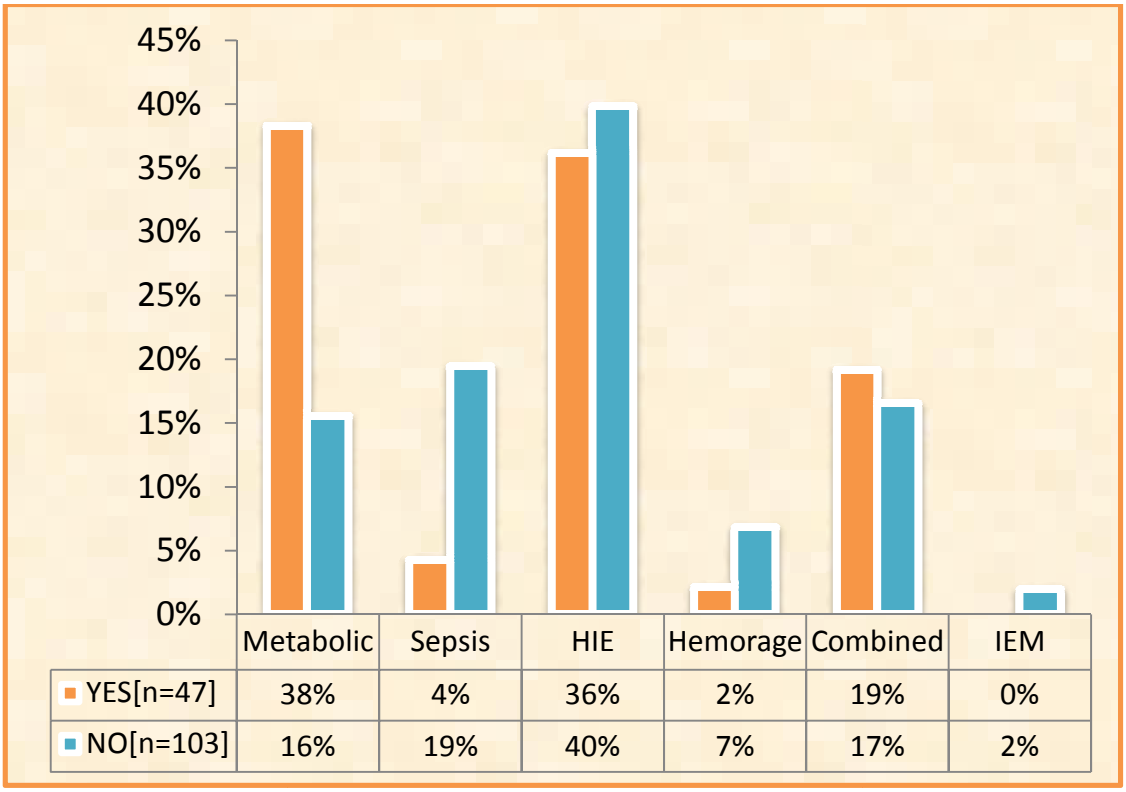
Followed by sepsis which is actually included in the combined group and in this group hypoglycaemia is the most common.

11. ASSOCIATION OF HYPOCALCEMIA WITH ESTABLISHED CAUSE OF SEIZURE

Table 9 : Association of hypocalcemia with established cause of seizure

Causes	Hypocalcemia		TOTAL	(%)
	YES	NO		
Metabolic	18	16	34	23%
Sepsis	2	20	22	15%
HIE	17	41	58	39%
Haemorrhage	1	7	8	5%
Combined	9	17	26	17%
IEM	0	2	2	1%
TOTAL	47	103	150	

In our study 39 % of HIE is associated with hypocalcemia and 23% of metabolic cause has association to hypocalcemia followed by combined and sepsis cause which are associated with hypocalcemia 17% and 15% respectively.



	Metabolic	Sepsis	HIE	Hemorage	Combined	IEM
YES[n=47]	38%	4%	36%	2%	19%	0%
NO[n=103]	16%	19%	40%	7%	17%	2%

Fig 22: Association of hypocalcemia with established cause of seizure

In our study among the total 47 cases of hypocalcemia, hypocalcemia is most commonly associated with HIE (39%)

12. ASSOCIATION OF HYPOMAGNESEMIA WITH ESTABLISHED CAUSE OF SEIZURE

Table 10 : Association of hypomagnesemia with established cause of seizure

Causes	Hypomagnesemia		TOTAL	(%)
	YES	NO		
Metabolic	5	29	34	23%
Sepsis	0	22	22	15%
HIE	1	57	58	39%
Haemorrhage	0	8	8	5%
Combined	1	25	26	17%
IEM	0	2	2	1%
TOTAL	7	143	150	

In 7 cases of hypocalcemic - hypomagnesemia 5 cases are associated and stands as an isolated metabolic cause for seizure.

1 out of 7 of hypocalcemic-hypomagnesemia associated with sepsis.

1 out of 7 is an isolated hypomagnesemia.

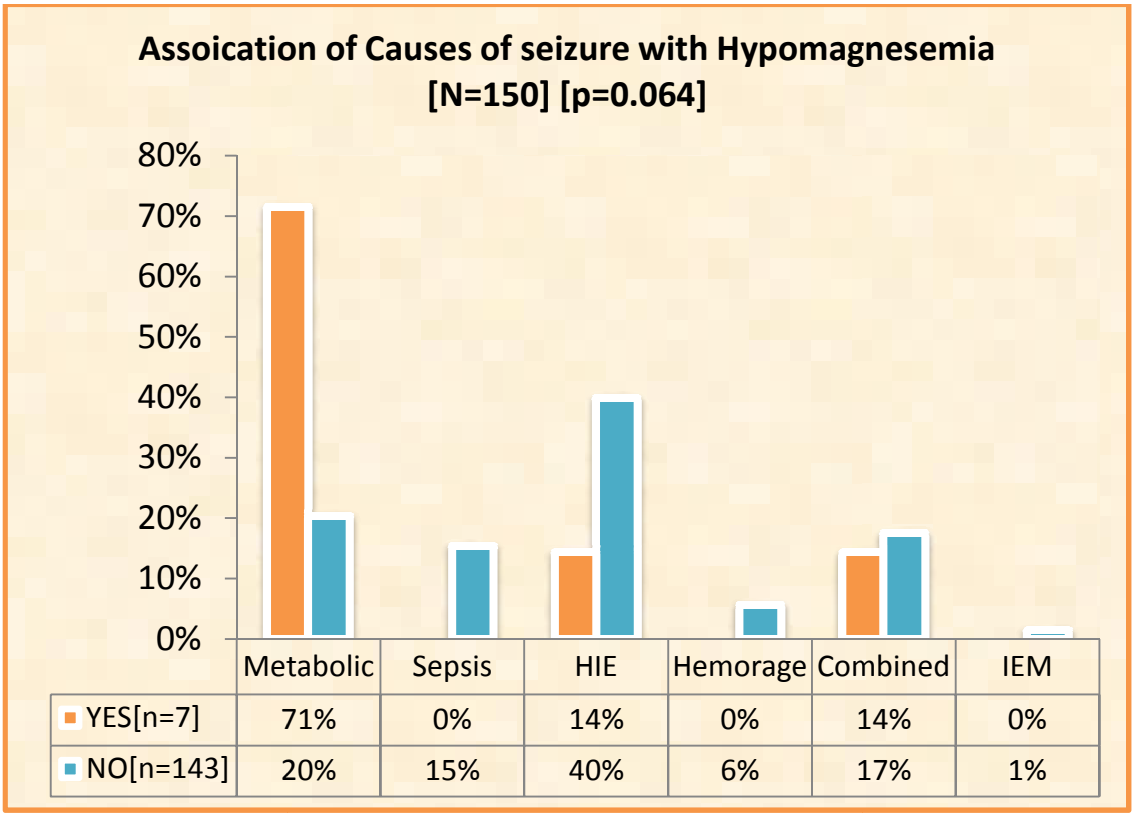
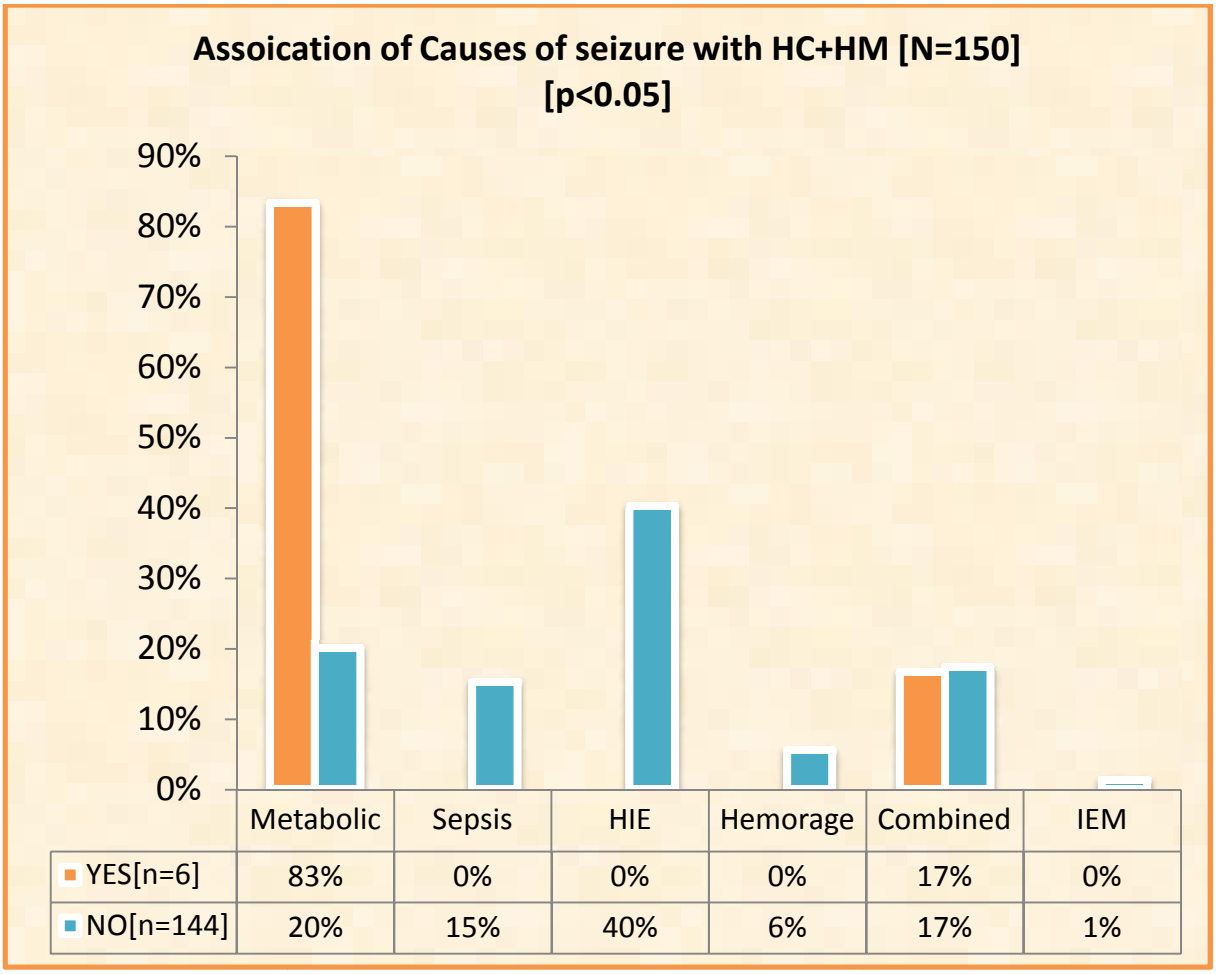


Fig 23: Association of hypomagnesemia with established cause of seizure

Hypomagnesemia is almost associated with hypocalcemia and other common associations are with sepsis and HIE.

13. ASSOCIATION OF HYPOCALCEMIC-HYPOMAGNESEMIA WITH ESTABLISHED CAUSE OF SEIZURE

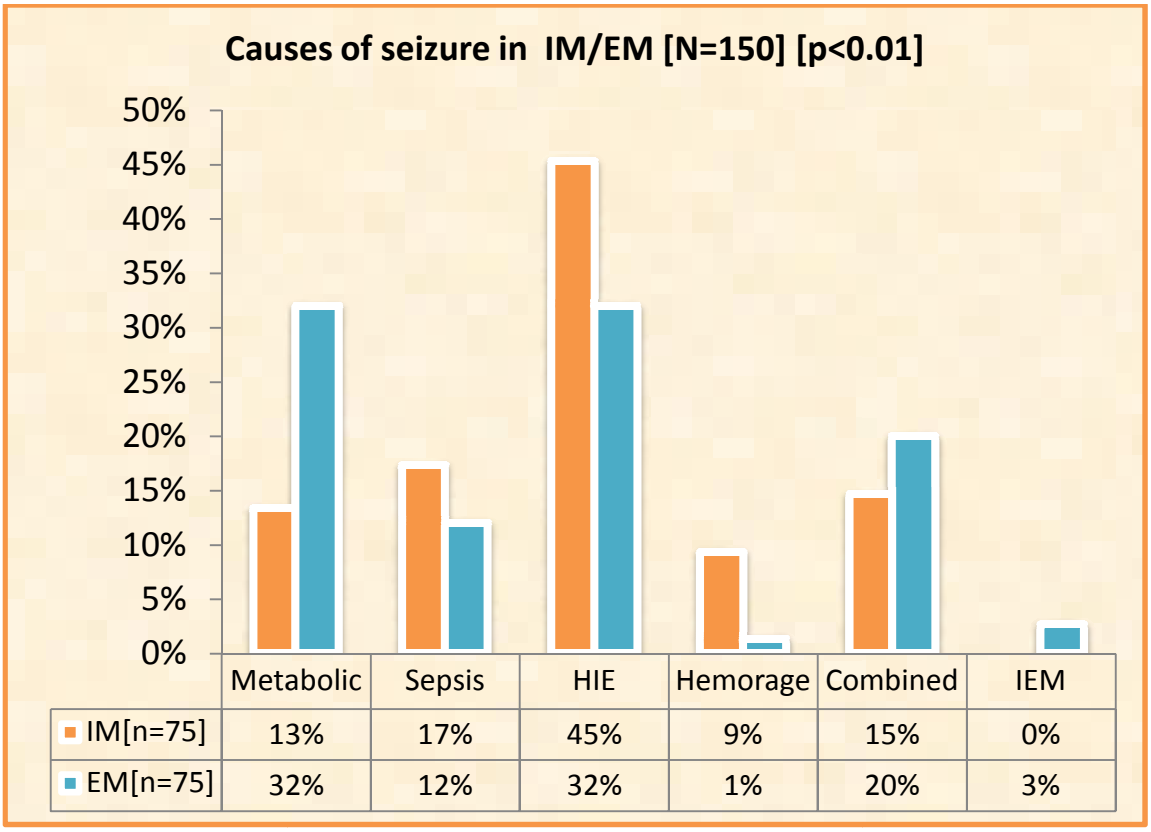


	Metabolic	Sepsis	HIE	Hemorage	Combined	IEM
YES[n=6]	83%	0%	0%	0%	17%	0%
NO[n=144]	20%	15%	40%	6%	17%	1%

Fig 24 : Association of HC+HM with established cause of seizure

Among the 7 cases of hypomagnesemia 6 are associated with hypocalcemia and its is mostly metabolic cause leading to seizure occupying around 85% .

14. MOST COMMON CAUSE OF SEIZURE IN INTRAMURAL AND EXTRAMURAL GROUP

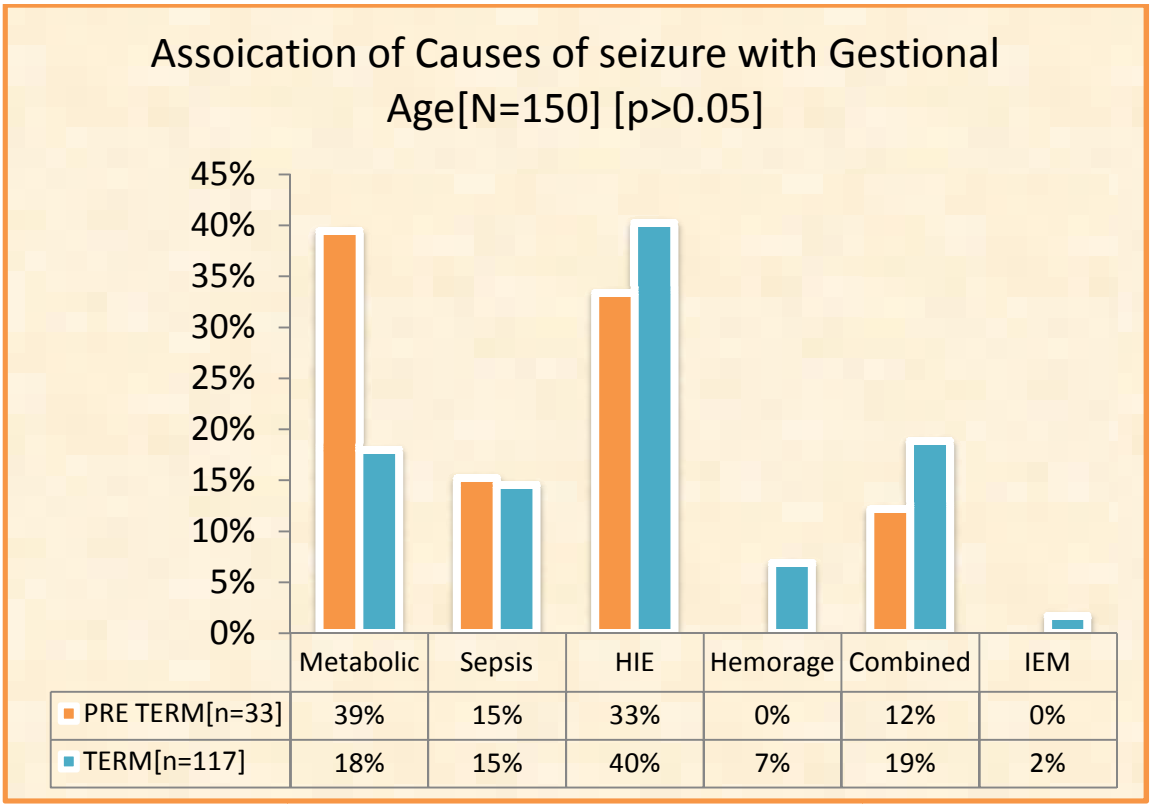


	Metabolic	Sepsis	HIE	Hemorage	Combined	IEM
IM[n=75]	13%	17%	45%	9%	15%	0%
EM[n=75]	32%	12%	32%	1%	20%	3%

Fig 25: Most common cause of seizure in intramural and extramural group

In the selected group of 150 the most common cause seizures in both intramural and extramural group is HIE which occupies 45% and 32% respectively. This implies that HIE is the most common cause seizures among neonatal seizures.

15. ASSOCIATION OF CAUSE OF SEIZURE WITH GESTATIONAL AGE



	Metabolic	Sepsis	HIE	Hemorage	Combined	IEM
PRE TERM[n=33]	39%	15%	33%	0%	12%	0%
TERM[n=117]	18%	15%	40%	7%	19%	2%

Fig 26 : Association of cause of seizure with gestational age

From the study it is inferred that metabolic abnormality are the most common cause of seizures in pre term group around 39% followed by HIE of 33% and in term group HIE is the most common cause around 40%.

DISCUSSION

In our study 150 neonates were included who presented with seizures to us for the first time both intramural and extramural according to the inclusion and exclusion criteria, and investigations proceeded as discussed in methodology.

Results of our primary objective:

In our study the prevalence of hypomagnesemia among 150 selected neonates with seizures is 4.6%.

Association of hypocaclcemia and hypomagnesemia

- Among the total 7 in 150, all 6 cases were associated with hypocalemia
- 85% of hypomagnesemia is associated with hypocalcemia
- Among the 5 out of 6 in hypocalcemic- hypomagnesemia stands as an isolated metabolic cause of seizure.
- And another 1 out of 6 in hypocalcemic-hypomagnesemia is associated with sepsis

- 1 out of 7 in hypomagnesemia is associated with HIE and it is an isolated hypomagnesemia without hypocalcemia.

- So hypomagnesemia is almost associated with hypocalcemia and other common causes of association with hypomagnesemia are sepsis and HIE.

Among the 7 cases of hypomagnesemia 6 is associated with hypocalcemia. The rate of association of hypomagnesemia with hypocalcemia is 85%.

Compaision of hypocalcemic-hypomagnesemia prevalence with other studies is shown in the following table:

Table 11: Prevalence of Hypocalcemia and hypomagnesemia comparision of studies

Studies	Hypocalcemia		Hypomagnesemia		Combined	
	N	%	N	%	N	%
Present study	18	52.9	7	20.5	6	17.6
Kumar et al.	5	55.5	1	11.1	-	-
Arvind sood et al.	7	70	3	30	-	-
Ronengabreil et al.	-	-	-	-	5	29.4
Ajay kumar et al.	9	42.8	-	-	1	4.7
Hatan tekgul et al.	-	-	-	-	1	33.3

All the studies quoted above including our present study had a small sample size and the correlation results were statistically insignificant, so there is need for a research to find the association of hypocalcemia and hypomagnesemia with a large size of sample group and over a longer duration.

Results derived from the study:

From the observations made the following results were derived as secondary results in our study

1. Distribution of cause of seizure in the study group:

Among the selected study group the most common cause seizures are Hypoxic ischemic encephalopathy (38.7 %) followed by Metabolic causes (22.7%)and Sepsis/Meningitis (14.75%) and intracranial bleed / IEM occupies the least common etiology.

Significant proportion of group is occupied by combined cause which is around 17.3% mainly sepsis combined with electrolyte abnormalities.

In a study on neonatal seizures by Moayedi AR et al., etiology of neonatal seizures was HIE (36.4%) followed by infections (19.1%), metabolic disorders (7.3%), ICH (2.7%) and structural disorders (1.8%).

In 32.7% cases etiology was not identified. This study had findings similar to our study.

Based on different studies conducted HIE is the most common cause of neonatal seizures followed by infections and metabolic causes. Seizures due to haemorrhage and inborn errors of metabolism are least.

Comparison of cause of seizures with other studies:

Table 12: Comparison of cause of seizures with other studies

Study group	HIE		Infection		Metabolic		others	
	N	%	N	%	N	%	N	%
Present study	58	38.7	22	14.7	34	22.7	36	24
Ajay kumar et al.	40	44.4	7	7.7	21	23.3	22	14
Moyaedi AR et al.	40	36.4	21	19.1	8	7.3	41	27
Hatan Tekgul et al.	36	40.4	3	3.3	5	5-6	30	20
Lakhra Mahaveer et al.	21	33	18	28	19	30	6	6
Sandhan Ravneet et al.	34	42.5	17	21.2	20	25	9	9
Brunqell Phillip et al.	26	49	1	2	1	2	25	16.6

2. Distribution of age /gender in the study group

- Seizures in <5 days age group occupies 79%, 5-10 days age group and 11-15 days age group occupies 10% and 9% respectively.

- In the selected group during the study period there is slight male preponderance in the occurrence of seizures with males occupying 59% and female child 41%.

Neonatal seizures have no sex predilection. However, in our study, male to female ratio was 1.43:1, similar with the study of neonatal seizures by Zakeri S et al. where male to female ratio was 1.3:1. The study of neonatal seizures by Hasan Tekgul et al. showed male to female ratio of 1.15:1.

Most common age group for the seizure occurrence in our study group is <5 days age group in which seizure on first day is almost 40%. In a study of neonatal seizures by Ronen Gabriel et al. onset of seizures on first day of life was 36%, 64% had onset of seizures within first 48 hours and 83% within first week of life, which is similar to our study. Onset of seizures within first 5 days constitutes the majority of cases, more so within first 48 hours of life.

3. Mean age of occurrence of seizure:

The mean age of occurrence of seizure among males is 4.28 days and mean age for female is 3.54 days but it is statistically insignificant. And the mean age of occurrence of seizures in the total group is 3.98 days, which in favours that the insults in earlier days are more severe and leads to long term sequale.

4. Comparison of Gestational age with seizures

In the study group of 150 selected, term babies occupies 78% of the total and 22% of the total is preterm babies.

Similar observations was seen in study by Moayedi AR et al. where term AGA babies were 83.6% and preterm were 12.7% and post term 3.6%. Study by Ravneet Sandhu et al. where term AGA babies were 81.2% followed by preterm babies in 18.8% which is similar to our study.

5. Biochemical abnormality in study group

Though there is an established cause for seizures metabolic abnormalities are associated in 79 cases out of 116 (68%) and, 34 cases had isolated metabolic abnormality as cause for seizure.

Among the associated metabolic abnormality hypoglycaemia and hypocalcemia are the most common with 31% of each, followed by hyponatremia and hypomagnesemia occupying 7% each.

Among the selected group HIE is most commonly associated with other biochemical abnormalities that is around 28 cases out of 58 are associated with biochemical abnormalities and hypocalcemia is the most common metabolic abnormality associated with HIE

Followed by sepsis which is actually included in the combined group and in this group hypoglycaemia is the most common association.

The most common disease to be associatedwith metabolic bnormality is HIE. The most common metabolic abnormality to be associated is hypocalcemia and hypoglycemia .39 % of HIE is associated with hypocalcemia and 23% of metabolic cause has association to hypocalcemia followed by combined and sepsis group which are associated with hypocalcemia 17% and 15% respectively.

6. Cause of seizure in intramural and extramural group:

In the selected group of 150 the most common cause seizures in both intramural and extramural group is HIE which occupies 45% and 32% respectively which implies that HIE is the most common cause seizures among neonatal seizures.

7. Cause of seizure in association with gestational age:

From the study it is inferred that metabolic abnormality are the most common cause of seizures in pre term group around 39% followed by HIE of 33% and in term group HIE is the most common cause around 40%.

SUMMARY

- A group of 150 neonates with seizures were studied
- Total of 7 cases had hypomagnesemia
- Among the total 7 hypomagnesemia cases in 150, all 6 cases were associated with hypocalemia
- 85% of hypomagnesemia is associated with hypocalcemia
- Among the 5 out of 6 in hypocalcemic- hypomagnesemia stands as an isolated metabolic cause of seizure.
- And another 1 out of 6 in hypocalcemic-hypomagnesemia is associated with sepsis
- 1 out of 7 in total hypomagnesemia is associated with HIE and it is an isolated hypomagnesemia without hypocalcemia.
- The prevalence of hypomagnesemia in study group is 4.6%
- The prevalence of hypocalcemic-hypomagnesemia is 4%
- The prevalence of isolated hypomagnesemia is 0.6%
- The association of hypomagnesemia with hypocalcemia is statistically significant

- Most common cause of seizure is Hypoxic ischemic encephalopathy (38.7 %)
- Metabolic causes of seizure (22.7%) Sepsis/Meningitis as cause of seizure (14.75%) and intracranial bleed / IEM occupies the least common etiology.
- Significant proportion of group is occupied by combined cause which is around 17.3% mainly sepsis combined with electrolyte abnormalities.
- In the selected group during the study period there is slight male preponderance in the occurrence of seizures with males occupying 59% and female child 41%.
- In our study, male to female ratio was 1.43:1
- The mean age of occurrence of seizure among males is 4.28 days and mean age for female is 3.54 days but it is statistically insignificant.
- In the study group of 150 selected term babies occupies 78% of the total and 22% of the total is preterm babies.
- The most common disease to be associated with metabolic abnormality is HIE 48.2%

- The most common metabolic abnormality to be in associatio with other causes is hypocalcemia and hypoglycemia each 31%.
- Most common etiology in both intramural and extramural group is HIE which occupies 45% and 32% respectively.
- Most common etiology in pre term group is metabolic abnormality 39% followed by HIE of 33% and in term group HIE cause around 40%.

CONCLUSION

- Hypomagnesemia as isolated abnormality for cause of seizure, or as associated abnormality in underlying etiology is rare. But 83% of hypomagnesemia is associated with hypocalcemia implying the interrelation in pathophysiology. So in documented hypocalcemia there is a need to estimate the levels of magnesium to find the associated hypomagnesemia because treatment of hypomagnesemia is definitive with magnesium salts.

- Biochemical abnormalities are treatable and investigations for biochemical abnormality should be the first line of investigations, before starting anticonvulsants.

- However further studies are required with large number of cases to establish the rate of association of hypomagnesemia with hypocalcemia.

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ANNEXURE 1

PROFORMA

NAME: **IP NO**:

AGE(in hours/days**):** **DOB/TOB**:

SEX: MCH/FCH **MOD** : LN/LSCS/FORCEPS

GESTATIONAL AGE: **INDICATION**:

TERM/PRETERM (wks)

SGA/AGA/LGA/IUGR

BIRTH WEIGHT:

ADMISSION WT:

RESUSCITATION DETAILS:

Tactlie stimulation	Bag and Mask	Intubation	BMV- chest compressions

APGAR SCORE : 1 “ 5” NOT KNOWN

HC: **CC**: **LENGTH**:

MATERNAL H/O:

H/O ANY MATERNAL ILLNESS DURING PREGNANCY AND MEDICATIONS GIVEN:

S.NO	DISEASE	TREATMENT/SPECIFICATIONS
1	PIH / IMMINENT ECLAMPSIA	Anti hypertensives / Mgso4
2	GDM	Insulin / diet
3	APH	Placenta previa / abruption
4	PROM / PPROM	<12 hrs / >12 hrs
5	ANEMIA	On IFA tab/ Injection/ transfusion
6	MECONIUM STAINED	Yes/ no

TIME OF OCCURENCE OF FIRST EPISODE OF SEIZURES:

HOURS OF LIFE: DAYS:

CLINICAL EXAMINATION:

CVS:

RS:

P/A:

CNS:

Vitals :

Temp: HR: RR: $Spo_{2:}$

INVESTIGATIONS:

CBG VALUE AT THE TIME OF ADMISSION:

CBC: TC:

DC:

HB:

PLATLET:

CRP:

BLOOD C/S:

CSF STUDY:

CELL COUNT:

BIOCHEM: PROTEIN

SUGAR

GLOBULIN

CSF C/S

SERUM SODIUM:

SERUM POTASSIUM:

SERUM CALCIUM :

SERUM MAGNESIUM:

USG CRANIUM IF DONE:

Anticonvulsants needed to control seizures

Dextrose alone	
Dextrose + calcium	

Phenobarbitone 1st 2nd 3rd	
Phenobarbitone + phenytoin	
Midazolam infusion	

IF PRESENT :

Hypomagnesemia	
Hypocalcemia	
Hypomagnesemia+Hypocalcemia	
Hypoglycemia	
Hyponatremeia	

CONSENT FORM

Your child …… is being asked to be a participant is the research study titled **"STUDY TO EVALUATE THE PREVALENCE HYPOMAGNESEMIA IN NEONATAL CONVULSIONS"** in CMCH, Coimbatore, conducted by Dr.Vikneswari.K, Post graduate student, Department of Paediatrics, Coimbatore Medical College Hospital your Child is eligible after looking on the inclusion criteria. You can able any question you may have, before agreeing to participate.

RESEARCH BEING DONE: To determine the prevalence of hypomagnesemia in neonatal convulsions.

PURPOSE OF RESEARCH: To find association of seizure with hypomagnesemia.

PROCEDURE: Investigated as per protocol

DECLINE FROM PARTICIPATION: You have the option to decline from participation in the study existing protocol for your condition.

PRIVACY AND CONFIDENTIALITY: Privacy of the individuals will be respected and any information about your child provided by you during the study will be kept strictly confidential.

AUTHORIZATION TO PUBLISH RESULTS: Results of the study may be published for scientific purpose and / or presented to scientific groups; however your child will not be identified.

STATEMENT OF CONSENT:

I volunteer and consent my child to participate in the study. I have read the consent or it has been read to me. The study has been fully explained to me, and I may ask questions at any time.

…… ……

Signature / left thumb impression of parent Date:

ஒப்புதல் படிவம்

பெயர் :

வயது :

பாலினம் :

முகவரி :

அரசு கோவை மருத்துவக் கல்லூரியில் பொது மருத்துவ துறையில் பட்ட மேற்படிப்பு பயிலும் மாணவி **செல்வி கி. விக்னேஸ்வரி** அவர்கள் மேற்கொள்ளும் "**பச்சிளம் குழந்தைகளின் வலிப்பு நோயில் மெக்னீஸியம் குறைபாட்டின் கணக்களவு**" பற்றிய ஆய்வில் செய்முறை மற்றும் அனைத்து விளக்கங்களையும் கேட்டுக் கொண்டு எனது சந்தேகங்களை தெரிவுபடுத்திக் கொண்டேன் என்பதை தெரிவித்துக் கொள்கிறேன்.

நான் இந்த ஆய்வில் முழு சம்மதத்துடனும், சுய சிந்தனையுடனும் கலந்து கொள்ள சம்மதிக்கிறேன்.

இந்த ஆய்வில் என்னைப் பற்றிய அனைத்து விபரங்கள் பாதுகாக்கப் படுவதுடன் இதன் முடிவுகள் ஆய்விதழில் வெளியிடப்படுவதில் ஆட்சேபணை இல்லை என்பதை தெரிவித்துக் கொள்கிறேன். எந்த நேரத்திலும் இந்த ஆய்வில் இருந்து நான் விலகிக் கொள்ள எனக்கு உரிமை உண்டு என்பதையும் அறிவேன்.

இடம்

தேதி

KEY TO MASTER CHART:

Sex	M=Male F=Female
IM/EM	IM=intramural EM=Extramural
GA	GA- gestational age PT-Preterm , T-Term
B.Wt Ad.Wt	Birth weight Admission weight
Resuscitation details	N=Nil T=Tactile stimulation Step 1,2,3 is one,two,three cycle of Bag and mask ventilation respectively Step 4intubation
TOS	Time of onset of seizure
Investigations	TC-Total count WNL-within normal limits, s-sepsis Hb- haemoglobin, N-normal L- Low CRP-C reactive protein, P-positive N-Negative C/S – culture and sensitivity, G-growth NG-no growth CSF- cerebro spinal fluid analysis, N-Normal M-Meningitis Sr.Ca- serum calcium,Sr.Na-serum Sodium, Sr.Mg – Serum Magnesium, Sr.Sugar- serum sugar N=normal L=Low (as defined in methodology)

Cause of seizure	1.Metabolic 2.Sepsis 3.Hie 4.Hemorraghe 5.Combined 6.IEM
Drugs used to control seizure	1-dextrose alone 2-dextrose+calcium 3-Dextrose+calcium+Phenobarbitone 4.Dextrose+calcium+Phenobarbitone+Phenytoin 5.Requried midazolam
HG	Hypoglycemia
HC	Hypocalcemia
HN	Hyponatremia
HM	Hypomagnesemia
Y/N	Y-yes N-No

MASTER CHART

s no	Name	age	sex	IM/EM	GA	B.Wt	Ad.wt	resuscitation details(N,1,2,3,4,T)	apgar score	TOS	Investigations									Cause of seizure	drug	inference				
											CBC		CRP	Blood C/S	CSF	sr.Ca	sr.Na	Sr.Mg	sugar						
											TC	Hb														
			M,F		term=T pre=PT	<1kg=1 1-2.5=2 >2.5=3	<1kg=1 1-2.5=2 >2.5=3		< 3=1, 3-6=2, >7=3		WNl/ Sepsis	N/L	P/N	NG/G	N=Nrl Meningitis=M	N/L	N/L	N/L	N/L	metabolic=1, sepsis=2 HIE=3,hemorage=4 combined=5 IEM=6	Step 1,2,3,4,5	HG	HC	HN	HM	HC+HM
																						Y/N	Y/N	Y/N	Y/N	Y/N
1	B/o Devi	2	m	IM	T	3	3	N	3	2	N	L	N	NG	.	N	N	N	L	4	4	Y	N	N	N	N
2	B/o Deepa	11	F	EM	T	3	3	N	3	11	N	N	N	NG	N	N	N	N	N	IEM	2	N	N	N	N	N
3	B/o Rajathi	2	M	IM	T	3	3	N	3	2	S	N	P	NG	N	N	N	N	N	2	4	N	N	N	N	N
4	B/o Anantha lk	6	F	EM	T	3	3	N	3	6	S	L	P	G	N	L	N	N	L	5	1	Y	Y	N	N	N
5	B/o Nandhini	4	M	EM	PT	2	2	N	3	4	N	N	.	.	.	N	N	N	L	1	1	Y	N	N	N	N
6	B/o Saranya	3	M	IM	T	3	3	N	3	3	N	N	.	.	.	L	N	L	N	1	3	N	Y	N	Y	Y
7	B/o kasthuri	1	M	IM	T	2	2	T	2	1	N	N	.	.	.	N	L	N	N	3	3	Y	N	N	N	N
8	B/o Lakshmi	1	F	IM	T	3	3	4	1	1	N	N	.	.	.	N	N	N	N	3	5	N	N	N	N	N
9	B/o Thilagavathi	24	M	EM	T	2	2	N	3	24	S	N	N	G	M	L	N	N	N	5	2	N	Y	N	N	N
10	B/o Suseela	4	M	IM	PT	2	2	N	3	4	S	N	N	NG	M	N	N	N	N	2	3	N	N	N	N	N
11	B/o Revathy	13	M	EM	PT	2	2	N	3	14	S	N	P	G	N	N	N	N	L	5	3	Y	N	N	N	N
12	B/o s.revathy	1	M	IM	T	3	3	2	1	1	N	N	.	.	.	N	N	N	N	3	4	N	N	N	N	N
13	B/o Amirtham	1	M	IM	T	3	3	2	1	1	N	N	.	.	.	L	N	N	N	3	4	N	Y	N	N	N
14	B/o Anandhi	5	F	IM	T	3	3	N	3	5	S	N	N	NG	N	N	N	N	N	2	4	N	N	N	N	N
15	B/o Gokila	11	F	EM	T	3	2	N	3	11	S	N	P	NG	M	N	N	N	N	2	4	N	N	N	N	N
16	B/o Amudha	6	M	EM	T	3	3	N	3	6	S	N	P	G	M	L	N	N	L	5	1	Y	Y	N	N	N
17	B/o Rani	3	M	IM	T	3	3	N	3	3	S	N	P	NG	M	N	N	N	N	2	3	N	N	N	N	N
18	B/o Thangamani	4	F	IM	T	3	3	N	3	4	N	L	N	NG	.	N	N	N	N	4	4	N	N	N	N	N
19	B/o Stella	3	M	IM	T	3	3	N	3	3	N	L	N	NG	.	N	N	N	N	4	5	N	N	N	N	N
20	B/o Kaousalya	1	F	IM	PT	2	2	T	2	1	N	N	.	.	.	N	L	N	N	3	3	Y	N	N	N	N
21	B/o Yasodha	3	M	IM	T	3	3	N	3	3	N	N	.	.	.	L	N	L	N	1	4	N	Y	N	Y	Y
22	B/o pavithra	10	M	EM	PT	3	3	N	3	10	N	N	N	.	.	N	N	N	L	1	1	Y	N	N	N	N
23	B/o Poongodi	3	M	IM	T	3	3	N	3	3	N	N	.	.	.	L	N	N	N	1	2	N	Y	N	N	N
24	B/o Shanthi	2	F	EM	T	3	3	N	3	2	N	N	.	.	.	L	N	N	N	1	2	N	Y	N	N	N
25	B/o Rajeswari	1	M	IM	T	3	3	T	2	1	N	N	.	.	.	L	N	N	N	3	3	N	Y	N	N	N
26	B/o Jayanthi	1	M	EM	T	3	3	1	2	2	N	N	.	.	.	N	N	N	N	3	3	N	N	N	N	N
27	B/o Jayanthini	1	M	EM	T	3	3	1	2	1	N	N	.	.	.	N	N	N	N	3	3	N	N	N	N	N
28	B/o Bhuvanes	4	M	EM	T	3	3	N	3	4	N	N	.	.	.	L	N	N	N	1	2	N	Y	N	N	N

s no	Name	age	sex	IM/EM	GA	B.Wt	Ad.wt	resuscitation details(N,1,2,3,4,T)	apgar score	TOS	Investigations									Cause of seizure	drug	inference				
											CBC		CRP	Blood C/S	CSF	sr.Ca	sr.Na	Sr.Mg	sugar			HG	HC	HN	HM	HC+HM
											TC	Hb														
			M,F		term=T pre=PT	<1kg=1 1-2.5=2 >2.5=3	<1kg=1 1-2.5=2 >2.5=3		< 3=1, 3-6=2, >7=3		WNl/ Sepsis	N/L	P/N	NG/G	N=Nrl Meningit is=M	N/L	N/L	N/L	N/L	metabolic=1, sepsis=2 HIE=3,hemorage=4 combined=5 IEM=6	Step 1,2,3,4,5	Y/N	Y/N	Y/N	Y/N	Y/N
29	B/o farzana	1	F	IM	T	3	3	3	1	1	N	N	.	.	.	N	N	N	N	3	4	N	N	N	N	N
30	B/o Muthu lk	1	F	EM	T	3	3	3	1	1	N	N	.	.	.	N	N	N	N	3	4	N	N	N	N	N
31	B/o Radhika	3	M	EM	T	3	3	N	3	5	S	N	P	G	N	N	N	N	N	2	1	N	N	N	N	N
32	B/o Sangeetha	12	F	EM	T	2	2	N	3	12	S	N	P	G	N	N	N	N	N	2	1	N	N	N	N	N
33	B/o Gowthami	8	M	EM	PT	2	2	N	3	9	S	L	P	NG	M	N	N	N	N	2	3	N	N	N	N	N
34	B/o Niramala	5	F	IM	T	2	2	N	3	7	S	N	P	NG	N	N	N	N	L	5	2	Y	N	N	N	N
35	B/o Mary	8	M	EM	PT	2	2	N	3	8	S	N	P	NG	M	N	N	N	N	2	4	N	N	N	N	N
36	B/o eswari	2	M	IM	T	3	3	N	3	2	S	N	P	NG	N	N	N	N	L	5	1	N	N	N	N	N
37	B/o Samsath	1	F	EM	T	3	3	2	1	1	N	N	.	.	.	N	N	N	N	3	4	N	N	N	N	N
38	B/o Poornima	12	M	EM	PT	3	3	N	3	12	N	N	N	.	.	N	N	N	L	1	1	Y	N	N	N	N
39	B/o Mallika	4	M	IM	T	3	3	N	3	4	N	N	.	.	.	N	N	N	L	1	1	Y	N	N	N	N
40	B/o Kaveri	2	F	IM	T	3	3	N	3	2	S	N	P	NG	N	N	N	N	L	5	1	Y	N	N	N	N
41	B/o jeeva	4	F	EM	T	3	3	N	3	4	S	N	P	G	N	L	N	N	L	5	2	Y	Y	N	N	N
42	B/o Sridevi	4	F	IM	PT	3	3	N	3	4	N	N	.	.	.	L	N	L	N	1	4	N	Y	N	Y	Y
43	B/0 Divya	6	M	EM	T	3	3	N	3	7	S	N	P	G	N	N	N	N	L	5	2	Y	N	N	N	N
44	B/o Ramani	1	F	IM	T	3	3	T	2	1	N	N	.	.	.	L	N	N	N	3	4	N	Y	N	N	N
45	B/o Kanmani	10	F	EM	PT	2	2	N	3	10	S	N	P	G	M	N	N	N	L	5	2	Y	N	N	N	N
46	B/o sasmitha	1	F	IM	PT	2	2	1	2	1	N	N	.	.	.	N	N	Y	N	3	4	N	N	N	Y	N
47	B/o Praba	1	M	IM	T	3	3	3	1	1	N	N	.	.	.	N	N	N	N	3	5	N	N	N	N	N
48	B/o Poornima	3	F	IM	T	3	3	N	3	3	S	L	P	NG	N	N	N	N	N	2	4	N	N	N	N	N
49	B/o Vasanthi	1	F	EM	PT	2	2	2	1	2	N	N	.	.	.	N	N	N	N	3	4	N	N	N	N	N
50	B/O thilaga	11	F	EM	T	3	2	N	3	11	N	N	N	.	.	N	N	N	L	N	2	Y	N	N	N	N
51	B/o savithri	2	M	EM	T	3	3	N	3	2	N	N	.	.	.	N	N	N	L	1	1	Y	N	N	N	N
52	B/o Ruckmani	23	M	EM	T	3	2	N	3	25	S	L	P	G	M	L	N	L	N	5	3	N	Y	N	Y	Y
53	B/O Ranjitha	1	F	IM	T	3	3	T	2	1	N	N	.	.	.	L	N	N	L	3	3	Y	Y	N	N	N
54	B/o vellaiamal	2	M	IM	T	3	3	N	3	2	N	N	N	NG	.	L	N	N	N	4	4	N	Y	N	N	N
55	B/o sajeena	1	M	EM	T	3	3	1	2	2	N	N	.	.	.	N	N	N	N	3	4	N	N	N	N	N
56	B/O thulasimani	1	F	IM	T	3	3	3	1	1	N	N	.	.	.	L	N	N	N	3	3	N	Y	N	N	N
57	B/o Ilaya	3	M	EM	PT	3	3	N	3	3	N	N	.	.	.	L	N	N	N	1	2	N	Y	N	N	N
58	B/o Yogapriya	1	F	EM	T	3	3	1	2	2	N	N	.	.	.	L	N	N	N	3	3	N	Y	N	N	N

s no	Name	age	sex	IM/EM	GA	B.Wt	Ad.wt	resuscitation details(N,1,2,3,4,T)	apgar score	TOS	Investigations									Cause of seizure	drug	inference				
											CBC		CRP	Blood C/S	CSF	sr.Ca	sr.Na	Sr.Mg	sugar			HG	HC	HN	HM	HC+HM
											TC	Hb														
			M,F		term=T pre=PT	<1kg=1 1-2.5=2 >2.5=3	<1kg=1 1-2.5=2 >2.5=3		< 3=1, 3-6=2, >7=3		WNl/ Sepsis	N/L	P/N	NG/G	N=Nrl Meningitis=M	N/L	N/L	N/L	N/L	metabolic=1, sepsis=2 HIE=3,hemorage=4 combined=5 IEM=6	Step 1,2,3,4,5	Y/N	Y/N	Y/N	Y/N	Y/N
59	B/o arulselvi	4	M	EM	T	3	3	N	3	4	N	L	N	NG	.	N	N	N	L	4	4	Y	N	N	N	N
60	B/o Gomathi	1	F	IM	T	3	3	1	2	1	N	N	.	.	.	N	N	N	N	3	4	N	N	N	N	N
61	B/oLavanya	4	F	EM	PT	3	3	N	3	4	N	N	N	.	.	N	N	N	L	1	1	Y	N	N	N	N
62	B/o Gurupriya	14	F	EM	T	3	3	N	3	14	N	N	N	NG	N	N	N	N	N	IEM	4	N	N	N	N	N
63	B/o Raji	2	F	EM	T	3	3	N	3	2	N	N	.	.	.	N	N	N	L	1	1	Y	N	N	N	N
64	B/o Amala	4	M	IM	T	3	3	N	3	4	N	N	.	.	.	L	N	N	N	1	2	N	Y	N	N	N
65	B/o Thangam	5	M	IM	T	3	3	N	3	5	S	N	P	G	N	N	L	N	N	5	3	N	N	Y	N	N
66	B/o Hema	1	M	EM	T	3	3	3	1	1	.	N	.	.	.	N	N	N	N	3	4	N	N	N	N	N
67	B/o Indira	3	M	EM	T	3	3	N	3	3	N	N	.	.	.	N	N	N	L	1	1	Y	N	N	N	N
68	B/o Lalitha	2	M	IM	T	3	3	N	3	2	N	L	N	NG	.	N	N	N	N	4	5	N	N	N	N	N
69	B/o Kalyani	2	F	IM	T	3	3	N	3	2	S	N	P	NG	N	N	N	N	L	5	1	Y	N	N	N	N
70	B/o Agalya	1	M	EM	T	3	3	3	1	1	N	N	.	.	.	N	N	N	N	3	4	N	N	N	N	N
71	B/o Saroja	1	M	IM	T	3	3	4	1	1	N	N	.	.	.	N	N	N	N	3	5	N	N	N	N	N
72	B/o Asmitha	1	M	EM	T	3	3	T	2	1	N	N	.	.	.	L	N	N	L	3	3	Y	Y	N	N	N
73	B/o Amirtham	5	F	EM	T	2	2	N	3	5	S	N	P	G	N	L	N	N	N	2	3	N	Y	N	N	N
74	B/o Preethi	2	M	IM	T	3	3	N	3	2	N	L	N	NG	.	N	N	N	L	4	4	Y	N	N	N	N
75	B/o Usha	5	F	IM	T	3	3	N	3	5	S	N	P	NG	N	N	L	N	N	5	3	N	N	Y	N	N
76	B/O preetha	1	F	EM	T	2	2	1	2	2	N	N	.	.	.	L	N	N	N	3	3	N	Y	N	N	N
77	B/oGomathi	2	M	IM	T	3	3	N	3	2	S	N	P	G	M	L	N	N	L	5	2	Y	Y	N	N	N
78	B/o ranjani	1	M	EM	T	3	3	T	2	1	N	N	.	.	.	N	N	N	N	3	3	N	N	N	N	N
79	B/o Anjali	4	M	EM	PT	3	3	N	3	4	N	N	N	.	.	L	N	N	L	1	2	Y	Y	N	N	N
80	B/o Chellam	2	F	IM	T	3	3	N	3	2	N	L	N	NG	.	N	N	N	N	4	4	N	N	N	N	N
81	B/o Suganthi	3	F	IM	T	3	3	N	3	3	S	N	P	NG	N	N	N	N	L	5	2	Y	N	N	N	N
82	B/o Gandhimati	1	M	IM	T	2	2	2	1	1	N	N	.	.	.	N	N	N	N	3	4	N	N	N	N	N
83	B/O Manju	2	F	IM	T	3	3	N	3	2	S	N	P	NG	N	N	N	N	N	2	4	N	N	N	N	N
84	B/o Parimala	4	M	IM	T	2	2	N	3	4	S	N	P	NG	M	N	L	N	N	2	4	N	N	Y	N	N
85	B/o Surya	2	M	IM	T	3	3	N	3	2	S	N	P	NG	N	L	N	N	N	2	4	N	Y	N	N	N
86	B/o Banu	2	F	IM	T	2	2	N	3	2	S	N	P	NG	M	N	N	N	N	2	4	N	N	N	N	N
87	B/o Suba	1	M	EM	T	3	3	1	2	1	N	N	.	.	.	N	N	N	N	3	3	N	N	N	N	N
88	B/o Rupa	1	M	IM	T	3	3	2	1	1	N	N	.	.	.	N	N	N	N	3	3	N	N	N	N	N

s no	Name	age	sex	IM/EM	GA	B.Wt	Ad.wt	resuscitation details(N,1,2,3,4,T)	apgar score	TOS	Investigations									Cause of seizure	drug	inference				
											CBC		CRP	Blood C/S	CSF	sr.Ca	sr.Na	Sr.Mg	sugar			HG	HC	HN	HM	HC+HM
											TC	Hb														
			M,F		term=T pre=PT	<1kg=1 1-2.5=2 >2.5=3	<1kg=1 1-2.5=2 >2.5=3		< 3=1, 3-6=2, >7=3		WNl/ Sepsis	N/L	P/N	NG/G	N=Nrl Meningitis=M	N/L	N/L	N/L	N/L	metabolic=1, sepsis=2 HIE=3,hemorage=4 combined=5 IEM=6	Step 1,2,3,4,5	Y/N	Y/N	Y/N	Y/N	Y/N
89	B/o Ragavi	4	F	IM	T	2	2	N	3	4	S	N	N	G	M	N	L	N	L	5	1	Y	N	Y	N	N
90	B/o sathyapriya	6	M	IM	T	3	3	N	3	6	N	N	.	.	.	N	N	N	L	1	1	Y	N	N	N	N
91	B/o Meenakshi	14	M	EM	T	3	2	N	3	14	S	N	P	NG	N	L	N	N	N	1	2	N	Y	N	N	N
92	B/o Sangeetha	1	M	IM	T	2	2	T	2	1	N	N	.	.	.	N	N	N	N	3	4	N	N	N	N	N
93	B/o Sasmi	7	F	EM	PT	2	2	N	3	7	S	L	P	NG	M	N	N	N	L	5	2	Y	N	N	N	N
94	B/o Rupa	1	M	IM	PT	2	2	2	1	1	N	N	.	.	.	N	N	N	N	3	5	N	N	N	N	N
95	B/o Kanmani	7	M	EM	T	2	2	N	3	8	S	L	P	NG	M	N	N	N	L	5	2	Y	N	N	N	N
96	B/o anbu	6	M	IM	PT	3	3	N	3	6	N	N	N	.	.	N	N	N	L	1	1	Y	N	N	N	N
97	B/o puspha	2	M	EM	PT	2	2	N	3	2	N	N	.	.	.	L	N	N	L	1	2	Y	Y	N	N	N
98	B/o rani	5	F	IM	PT	2	2	N	3	5	S	L	P	NG	M	N	N	N	L	5	3	Y	N	N	N	N
99	B/o Dharshini	1	F	EM	T	3	3	3	1	1	N	N	.	.	.	N	N	N	N	3	4	N	N	N	N	N
100	B/o Ruckmani	7	M	EM	T	3	3	N	3	7	S	L	N	NG	M	L	N	N	N	5	3	N	Y	N	N	N
101	B/o Anitha	1	F	IM	T	3	3	T	2	1	N	N	.	.	.	N	N	N	L	3	3	Y	Y	N	N	N
102	B/o Beulah	11	F	EM	T	3	3	N	3	11	S	N	P	G	M	N	N	N	N	2	4	N	N	N	N	N
103	B/o Banu	1	F	IM	T	3	3	2	1	1	N	N	.	.	.	N	N	N	N	3	4	N	N	N	N	N
104	B/o Chitra	1	M	IM	PT	2	2	1	2	1	N	N	.	.	.	N	N	N	N	3	3	N	N	N	N	N
105	B/o Kannagi	3	M	EM	T	3	3	N	3	3	N	N	.	.	.	N	N	N	L	1	1	Y	N	N	N	N
106	B/o Sumathi	1	M	IM	T	3	3	1	2	1	N	N	.	.	.	N	N	N	N	3	4	N	N	N	N	N
107	B/o Rasiya	1	M	EM	T	3	3	3	1	1	N	N	.	.	.	N	N	N	N	3	5	N	N	N	N	N
108	B/o Sakthhi	1	F	IM	T	3	3	T	2	1	N	N	.	.	.	L	N	N	N	3	3	N	Y	N	N	N
109	B/o Divya	7	F	IM	T	3	3	N	3	7	N	N	N	.	.	N	N	N	L	1	1	Y	N	N	N	N
110	B/o Jothi	1	M	EM	T	3	3	3	1	1	N	N	.	.	.	L	N	N	N	3	4	N	Y	N	N	N
111	B/o Yasmin	11	M	EM	PT	2	2	N	3	12	S	N	P	NG	M	N	N	N	N	2	4	N	N	N	N	N
112	B/o Saradha	1	M	IM	T	3	3	T	2	1	N	N	.	.	.	N	N	N	N	3	4	N	N	N	N	N
113	B/o hajira	1	M	EM	T	3	3	1	2	2	N	N	.	.	.	N	N	N	N	3	3	N	N	N	N	N
114	B/o Susi	8	M	EM	T	3	3	N	3	8	S	L	P	NG	M	N	N	N	N	2	4	N	N	N	N	N
115	B/o Akani	1	M	EM	PT	2	2	4	1	1	N	N	.	.	.	N	L	N	N	3	5	N	N	Y	N	N
116	B/o Samta	3	M	EM	T	3	3	N	3	3	N	N	.	.	.	L	N	N	N	1	2	N	Y	N	N	N
117	B/o Anitha	12	M	EM	PT	2	2	N	3	12	S	N	P	NG	N	N	N	N	L	1	1	Y	N	N	N	N
118	B/o Poornima	1	F	IM	T	3	3	3	1	1	N	N	.	.	.	N	N	N	N	3	4	N	N	N	N	N

s no	Name	age	sex	IM/EM	GA	B.Wt	Ad.wt	resuscitation details(N,1,2,3,4,T)	apgar score	TOS	Investigations									Cause of seizure	drug	inference				
											CBC		CRP	Blood C/S	CSF	sr.Ca	sr.Na	Sr.Mg	sugar	metabolic=1, sepsis=2 HIE=3,hemorage=4 combined=5 IEM=6	Step 1,2,3,4,5	HG	HC	HN	HM	HC+HM
											TC	Hb														
			M,F		term=T pre=PT	<1kg=1 1-2.5=2 >2.5=3	<1kg=1 1-2.5=2 >2.5=3		< 3=1, 3-6=2, >7=3		WNl/ Sepsis	N/L	P/N	NG/G	N=Nrl Meningitis=M	N/L	N/L	N/L	N/L			Y/N	Y/N	Y/N	Y/N	Y/N
119	B/o Sumi	20	M	EM	T	3	3	N	3	20	S	L	P	G	M	L	N	N	N	5	3	N	Y	N	N	N
120	B/o Yasmin	3	M	EM	PT	3	3	N	3	3	N	N	.	.	.	L	N	N	N	1	2	N	Y	N	N	N
121	B/o Saleema	1	M	EM	T	3	3	T	2	1	N	N	.	.	.	L	N	N	N	3	3	N	Y	N	N	N
122	B/o Baby	1	M	EM	PT	2	2	4	1	1	N	N	.	.	.	N	L	N	N	3	5	N	N	Y	N	N
123	B/o Chitra	1	M	IM	T	3	3	2	1	1	N	N	.	.	.	L	N	N	N	3	4	N	Y	N	N	N
124	B/o Sameena	4	M	IM	T	3	3	N	3	4	N	L	P	G	M	N	N	N	N	2	4	N	N	N	N	N
125	B/o Mano	1	F	IM	T	3	3	T	2	1	N	N	.	.	.	L	N	N	N	3	4	N	Y	N	N	N
126	B/o Karunya	1	F	IM	PT	2	2	1	2	1	N	N	.	.	.	N	N	N	N	3	3	N	N	N	N	N
127	B/o Kiruba	5	M	IM	T	3	3	N	3	5	N	N	.	.	.	L	N	L	N	1	3	N	Y	N	Y	Y
128	B/o Geetha	1	F	EM	PT	2	2	2	1	2	N	N	.	.	.	N	N	N	N	3	4	N	N	N	N	N
129	B/o eswari	4	M	IM	T	3	3	N	3	4	S	N	P	NG	M	N	N	N	L	5	1	Y	N	N	N	N
130	B/o Vani	3	F	EM	T	3	3	N	3	3	N	N	.	.	.	L	N	L	N	1	2	N	Y	N	Y	Y
131	B/o Divya	3	M	EM	T	3	3	N	3	3	N	N	.	.	.	L	N	N	N	1	2	N	Y	N	N	N
132	B/o Kirthika	11	M	EM	T	3	3	N	3	11	S	N	N	G	N	N	N	N	L	5	4	Y	N	N	N	N
133	B/o Kokila	1	M	IM	T	3	3	2	1	1	N	N	.	.	.	L	N	N	N	3	4	N	Y	N	N	N
134	B/o Jaya	5	F	EM	PT	3	3	N	3	5	N	N	N	.	.	L	N	N	N	1	2	N	Y	N	N	N
135	B/o chandra	1	M	EM	T	3	3	T	2	1	N	N	.	.	.	L	N	N	L	3	3	Y	Y	N	N	N
136	B/o Gayathri	3	M	EM	T	3	3	N	3	3	N	N	.	.	.	N	N	N	L	1	2	Y	N	N	N	N
137	B/o Raseena	11	M	EM	T	2	2	N	3	12	S	N	N	G	N	L	N	N	N	5	2	N	Y	N	N	N
138	B/o Mariammal	1	F	IM	T	3	3	2	1	1	N	N	.	.	.	L	N	N	N	3	4	N	Y	N	N	N
139	B/o aiyama	1	F	IM	T	3	3	4	1	1	N	N	.	.	.	N	N	N	N	3	5	N	N	N	N	N
140	B/o Anju	1	F	EM	T	3	3	1	2	2	N	N	.	.	.	N	L	N	N	3	4	Y	N	N	N	N
141	B/o Vennila	14	M	EM	T	3	2	N	3	14	S	N	P	G	M	N	N	N	L	5	2	Y	N	N	N	N
142	B/o Haseena	4	F	IM	T	3	3	N	3	4	S	L	P	G	M	N	N	N	N	2	4	N	N	N	N	N
143	B/o Gowri	3	M	EM	T	3	3	N	3	3	N	N	.	.	.	N	N	N	L	1	1	Y	N	N	N	N
144	B/o Gowthami	1	F	EM	PT	2	2	T	2	1	N	N	.	.	.	N	N	N	N	3	3	N	N	N	N	N
145	B/o Anju	5	F	IM	T	3	3	N	3	5	S	N	P	NG	N	N	N	N	N	2	3	N	N	N	N	N
146	B/o Geetha	1	M	IM	T	3	3	3	1	1	N	N	.	.	.	N	N	N	N	3	4	N	N	N	N	N
147	B/o Yogam	1	F	IM	T	3	3	4	1	1	N	N	.	.	.	N	N	N	N	3	5	N	N	N	N	N
148	B/o Ammu	3	F	EM	PT	3	3	N	3	3	N	N	.	.	.	L	N	N	N	1	3	N	Y	N	N	N
149	B/o rani	5	F	IM	PT	2	2	N	3	5	S	N	P	NG	N	N	N	N	N	2	3	N	N	N	N	N
150	B/o Devi	1	M	IM	PT	2	2	4	1	1	N	N	.	.	.	N	L	N	N	3	5	N	N	Y	N	N